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Innovations in Fluorescence

Frequency Domain Near-Infrared Spectroscopy. Clinical Applications for the Study of the Oxygenation and Hemodynamics of the Brain and Muscle

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OUTLINE

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  - ICU post operative monitoring
  - Obstructive Sleep Apnea Syndrome
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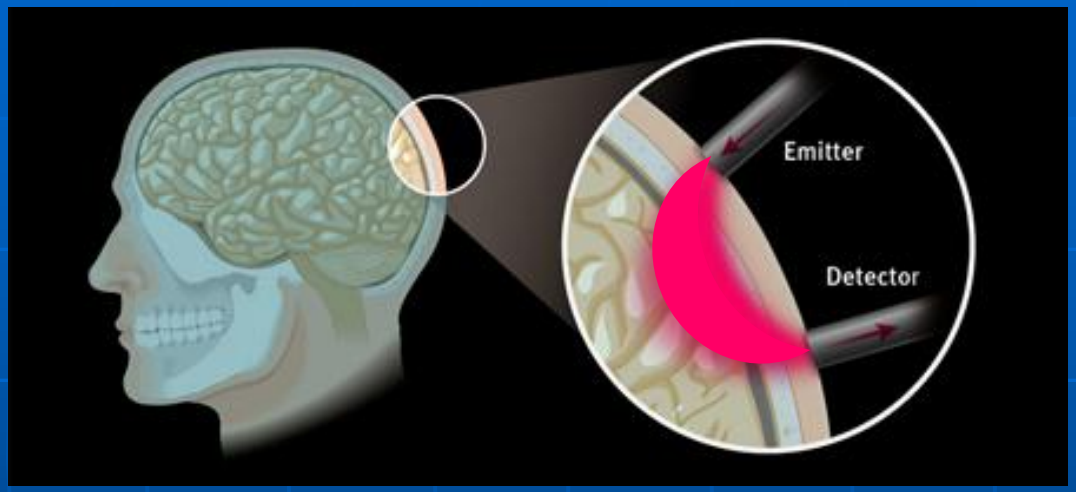
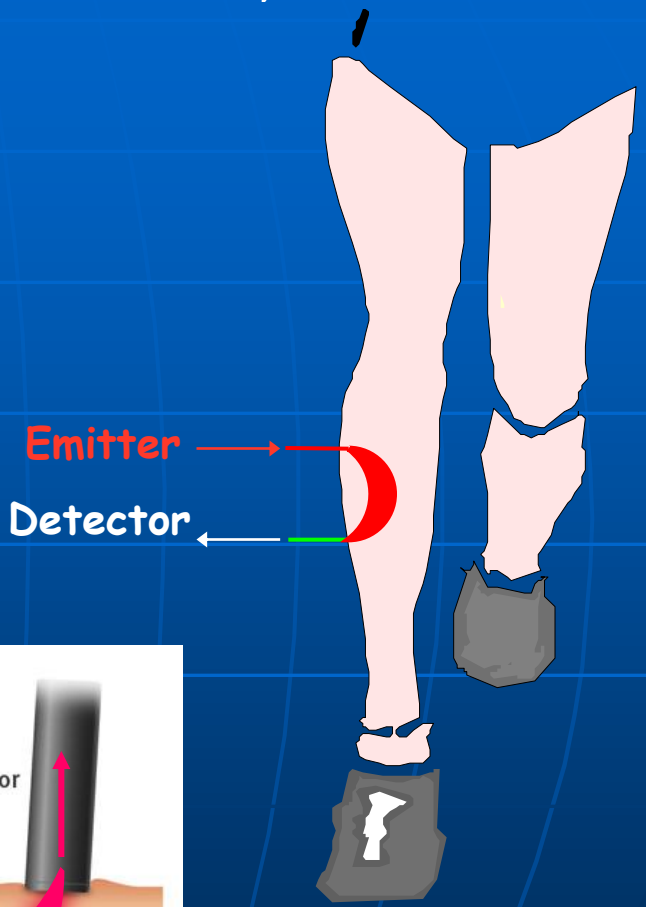
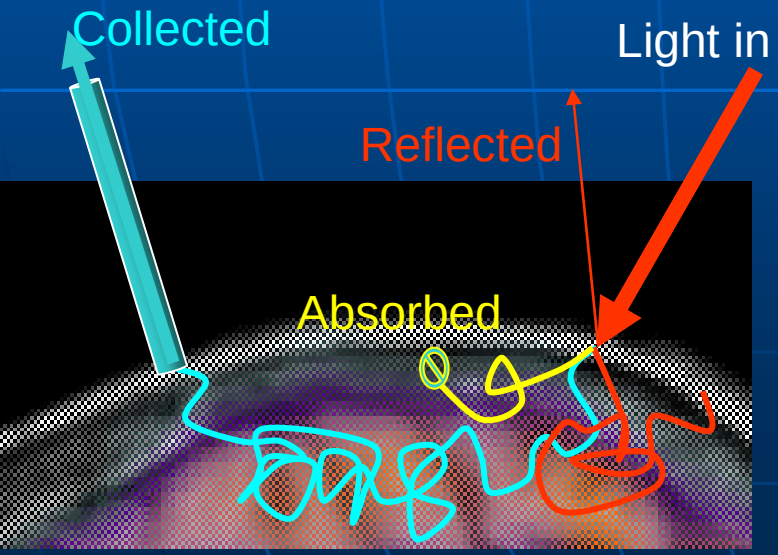
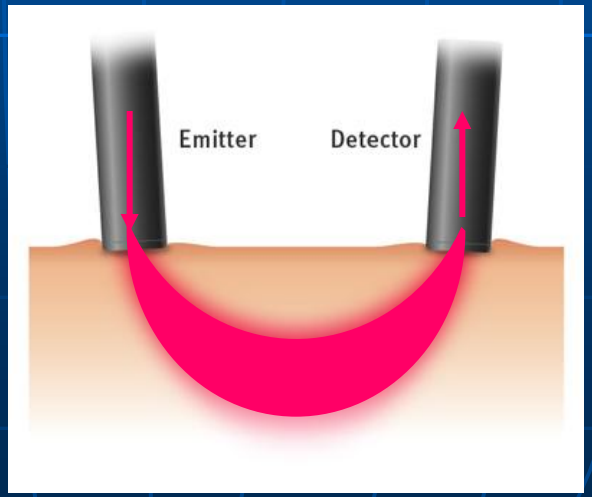
  - Activation of Brain Areas
  - Muscle Hemodynamic Changes in PVD

NIRS nel Dominio delle Frequenze. Applicazioni Cliniche della Spetroscopia e Ossimetria del Cervello e del Muscolo



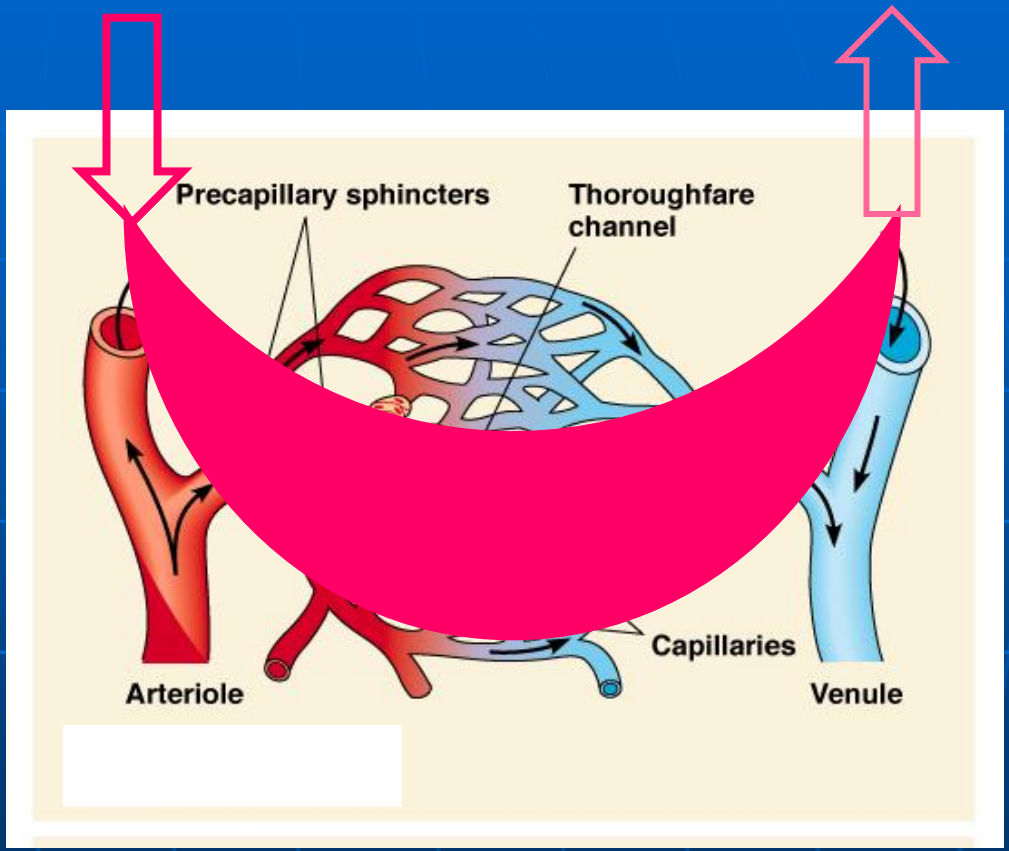






Why Near-Infrared Spectroscopy?

- Non-invasive
- Non-ionizing
- Comfortable
- Portable
- Cost effective
- Fast
- Reliable
- Real-time monitoring of tissue oxygenation and hemodynamics



Why Frequency Domain Near-Infrared Spectroscopy of Biological Tissues

FD-NIRS separates absorption from scattering to obtain absolute values of hemoglobin concentration and tissue oxygen saturation

Main NIRS parameters:

- Oxygenated hemoglobin, [O_2Hb]
- Deoxygenated hemoglobin, [HHb]
- Total hemoglobin, [tHb] = [O_2Hb]+ [HHb]
- Tissue oxygenation, SO_2=[O_2Hb]/[tHb]

Frequency-Domain Tissue Oximeter

(Developed at LFD-UIUC, Built by ISS Inc., Champaign, IL, USA).

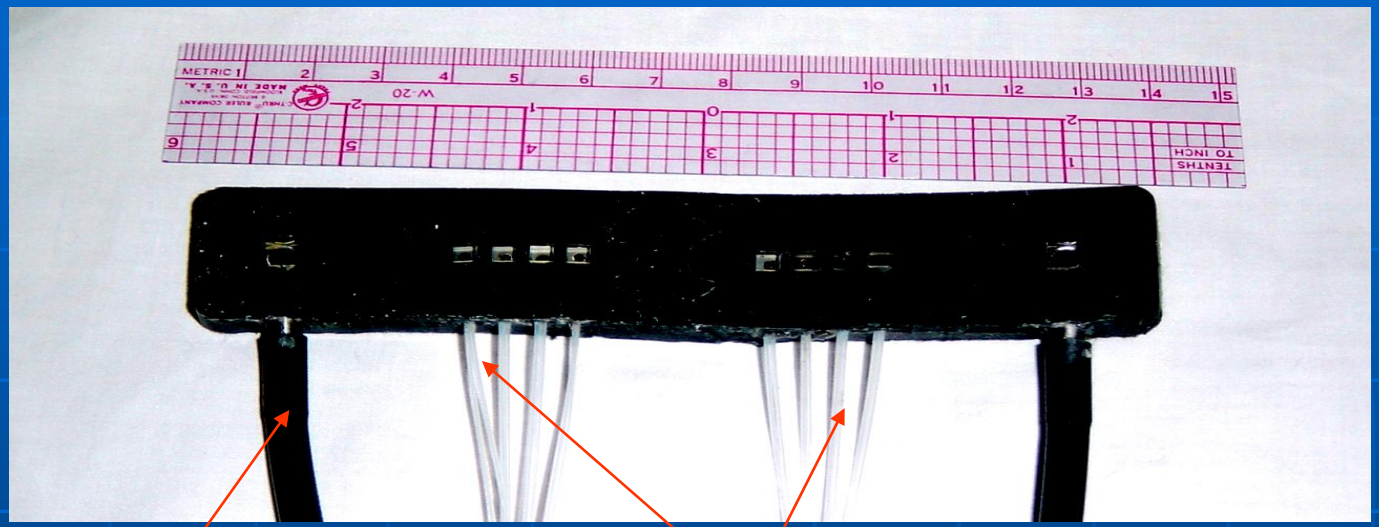
Modulation Frequency: 110 MHz

Light sources: 8 laser diodes at 690 nm
8 laser diodes at 830 nm
(electronically multiplexed at 40Hz)

Detectors: 2 photomultiplier tubes

Multi distance Method

Dual Sensor Probe
(for bilateral frontal lobe measurements)

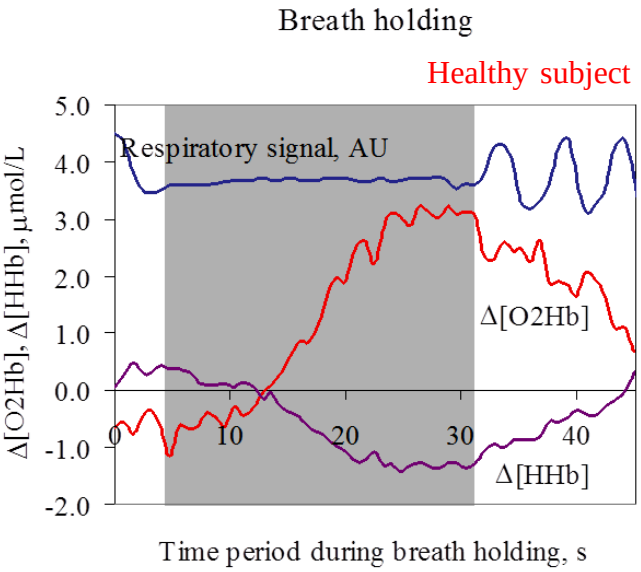


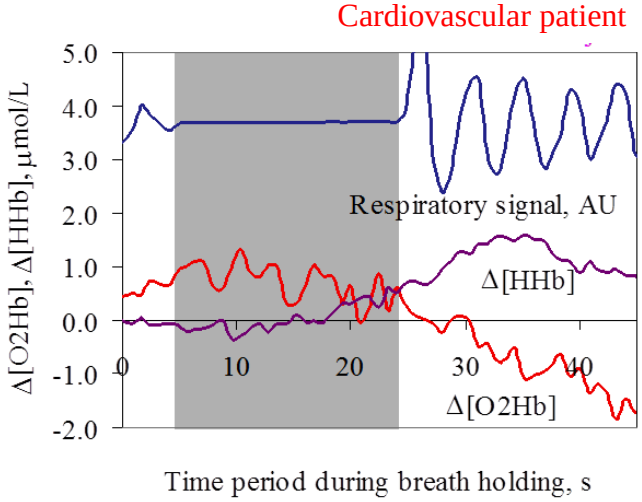
Detector fibers:1 per channel (3 mm internal diameter)

Source fibers:4 pairs of fibers (emitting 690 nm and 830 nm respectively) per channel

Source-detector distance: Range 2-4 cm
(multi-distance approach)

Cerebral hemodynamic changes during voluntary hypoxia





Hemodynamic responses to breath holding in a healthy individual

Increase in [O_2Hb]
Decrease in [HHb]

Altered Hemodynamic responses to breath holding in subject with severe cardiovascular disease.

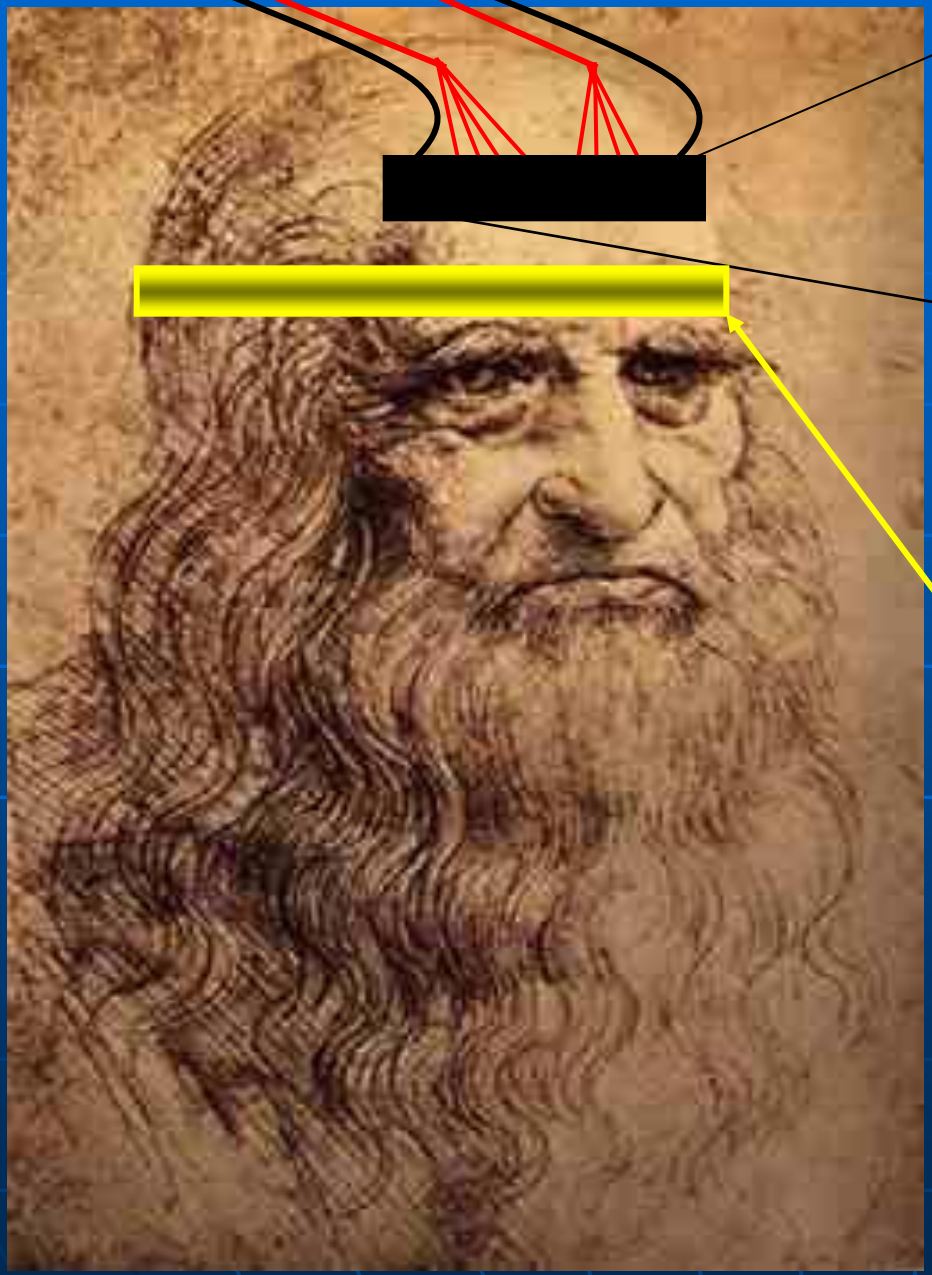
Decrease in [HHb]
Increase in [O2Hb]

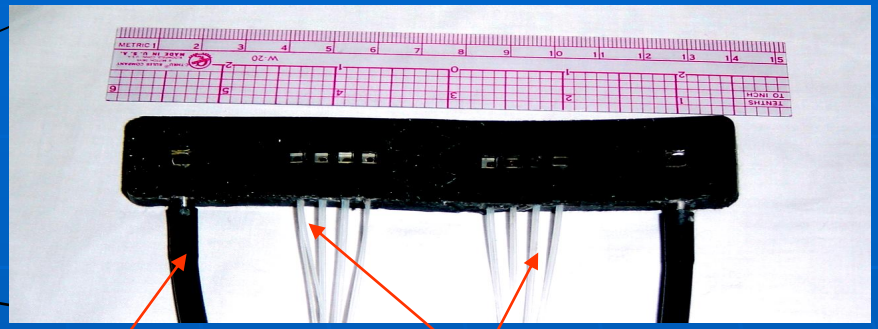
Questions from the medical community:

- Does the FD-NIRS and the multidistance approach probe the brain?
- Which are the appropriate source-detector distances?
- What proof can we give that the findings are not influenced by the superficial tissues.

Experimental approaches:

- Brain vascular responsiveness to voluntary hypoxia with and without partial scalp ischemia.
- Clamping of external and internal carotid arteries during neurovascular surgery





Detector fiber

Light source fibers

Partial scalp ischemia induced by a **head tourniquet**

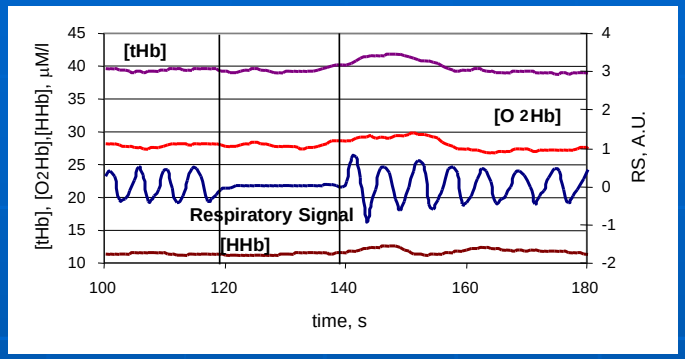
Breath Holding Exercises on 11 healthy volunteers

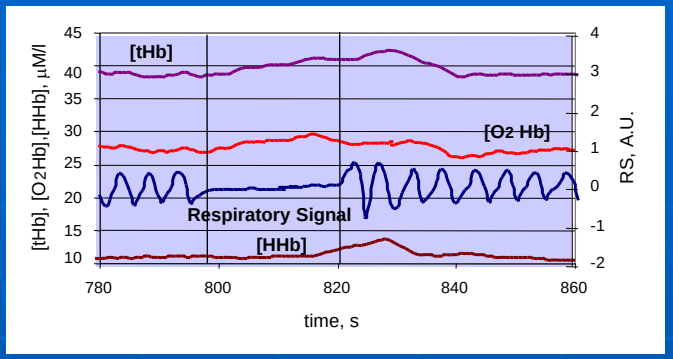
Without tourniquet

With tourniquet

Whole array SDD
1.08 cm-4.38 cm

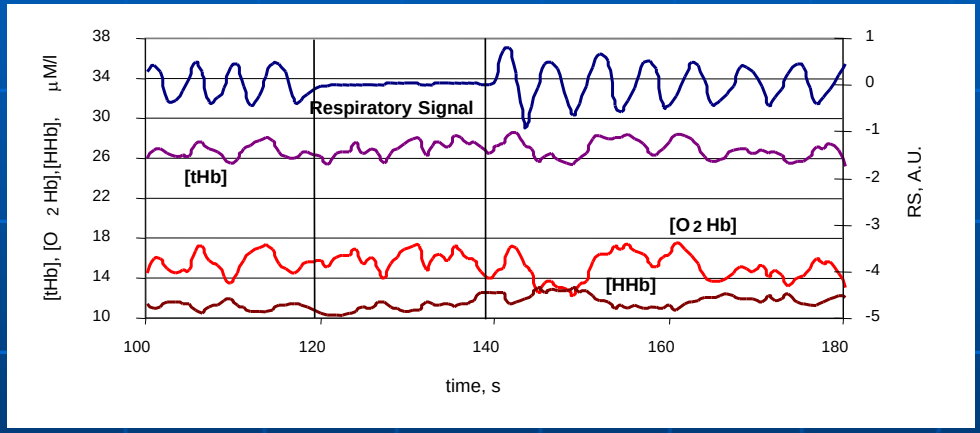
a)





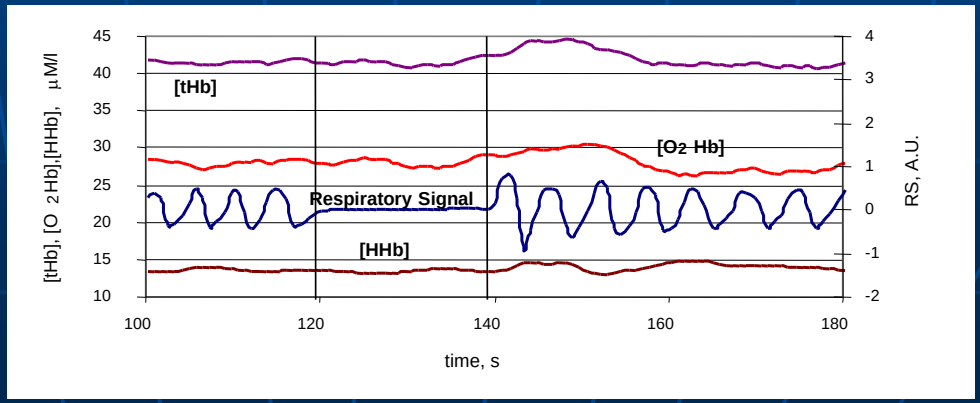
SDD
1.08 cm-1.98 cm
(Superficial Tissues)

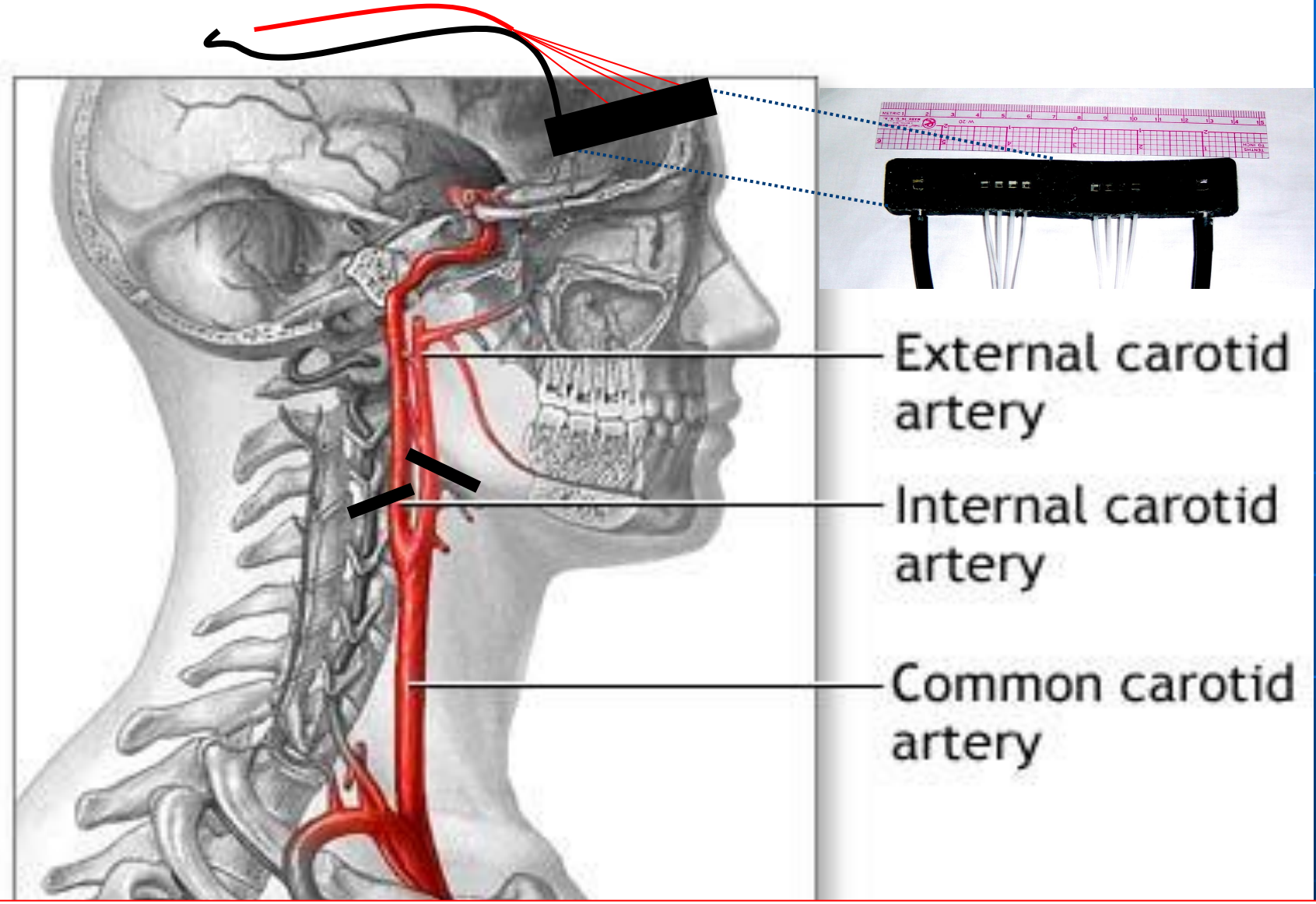
b)



SDD
1.98 cm-4.38 cm
(Deep Tissues)

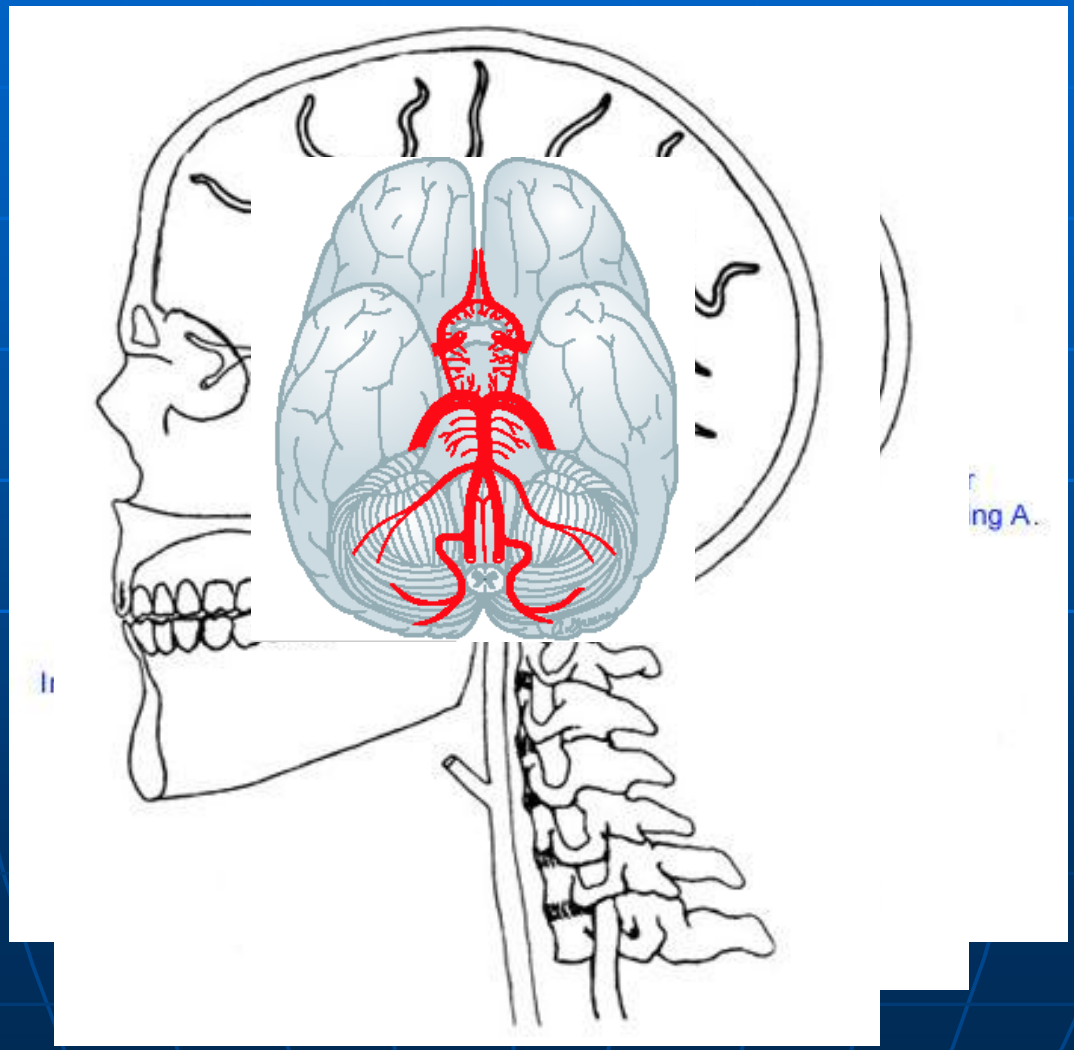
c)





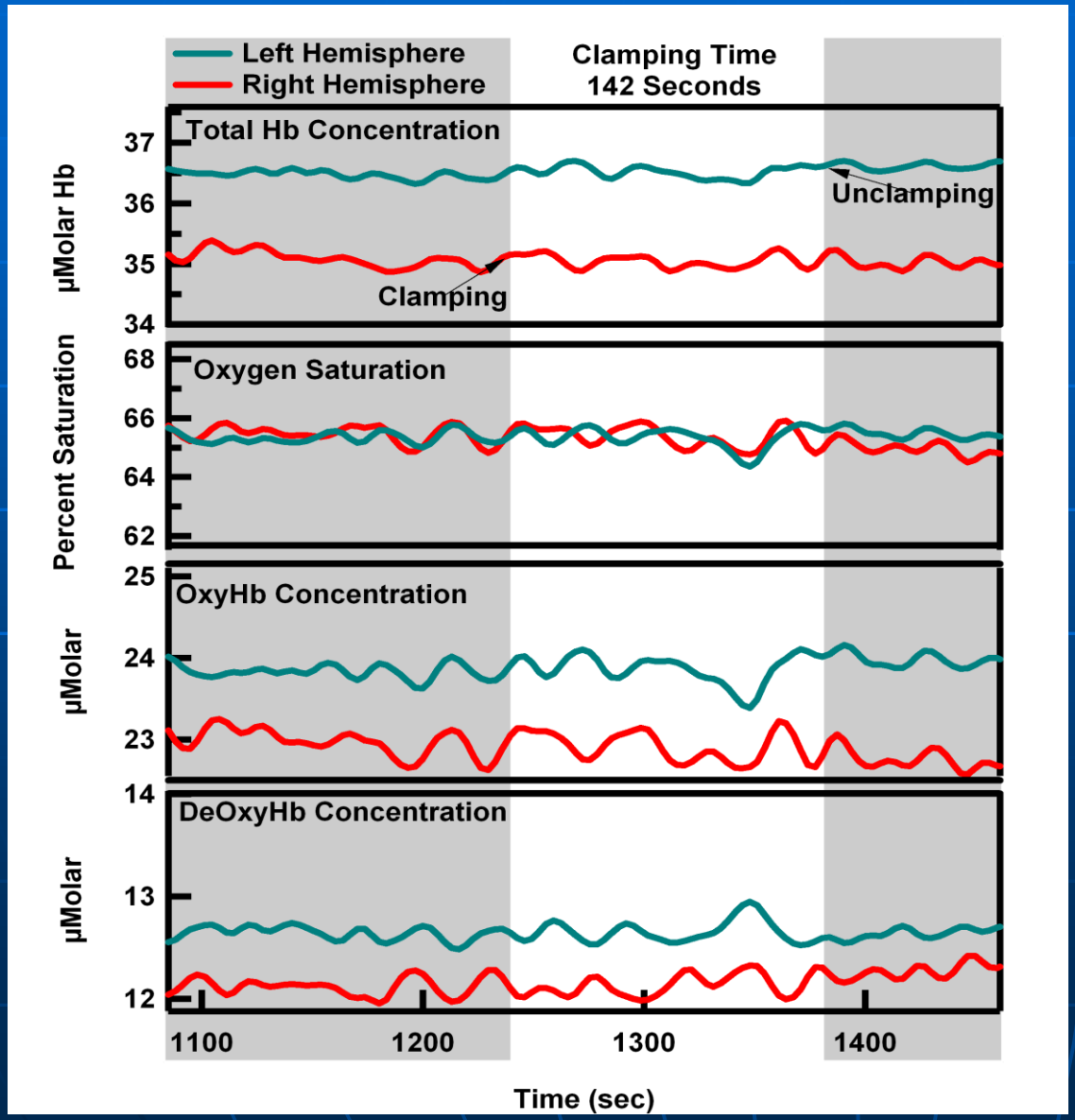
Clamping of External vs. Internal Carotid Artery
in a Patient with Defective Left to Right Brain Vascular Anastomotic Communication during Neurovascular Surgery

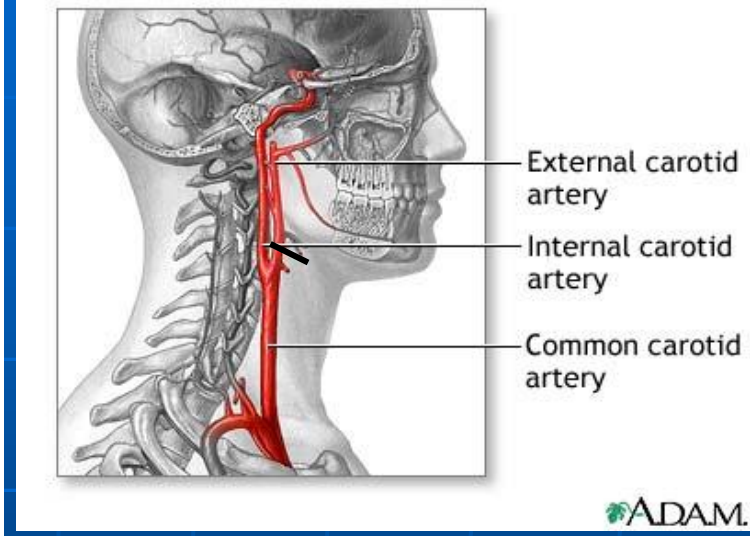
NORMAL BRAIN ARTERIAL CIRCULATION



External Carotid Artery Clamping

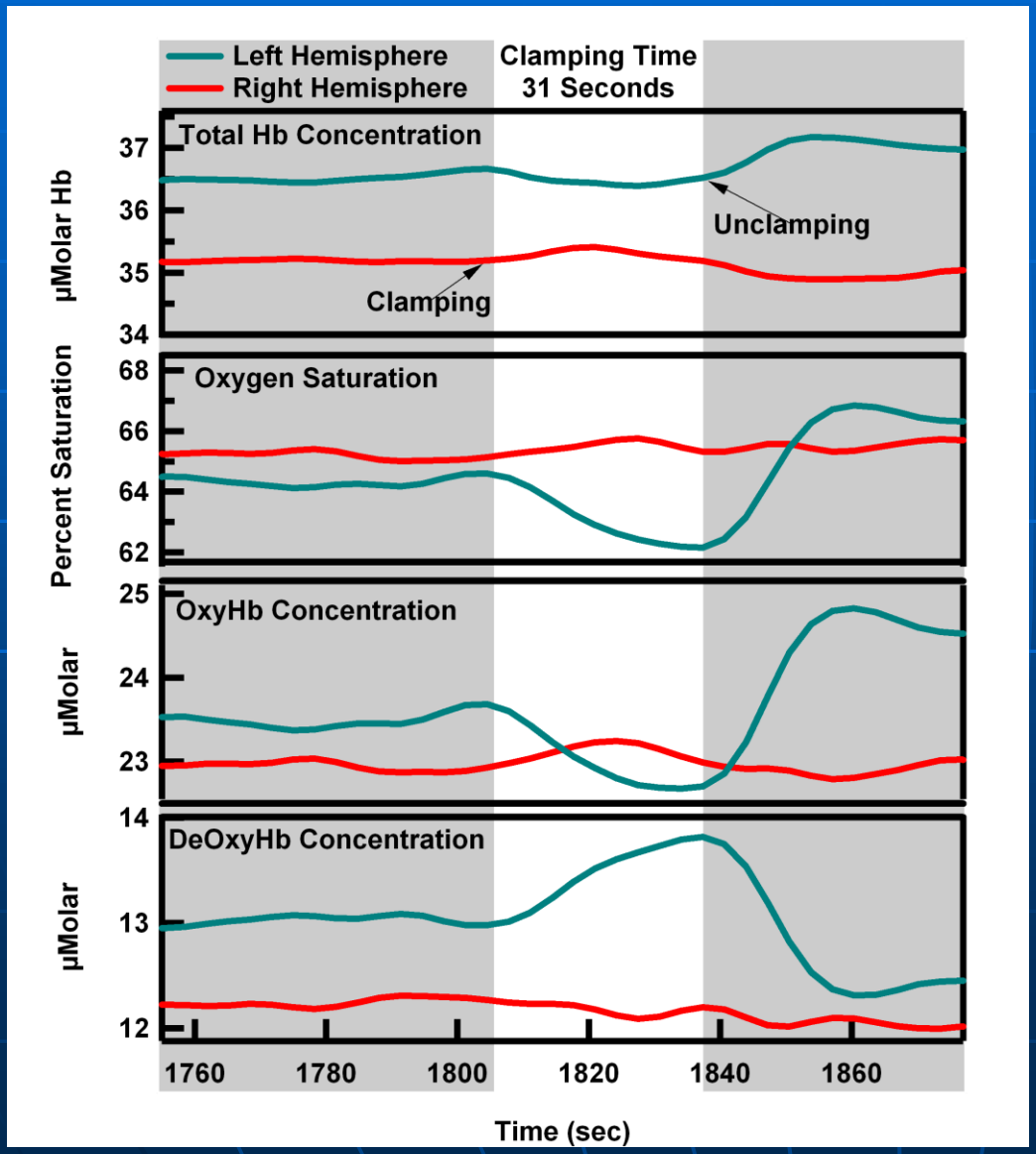
No change brain oxygenation and hemodynamics

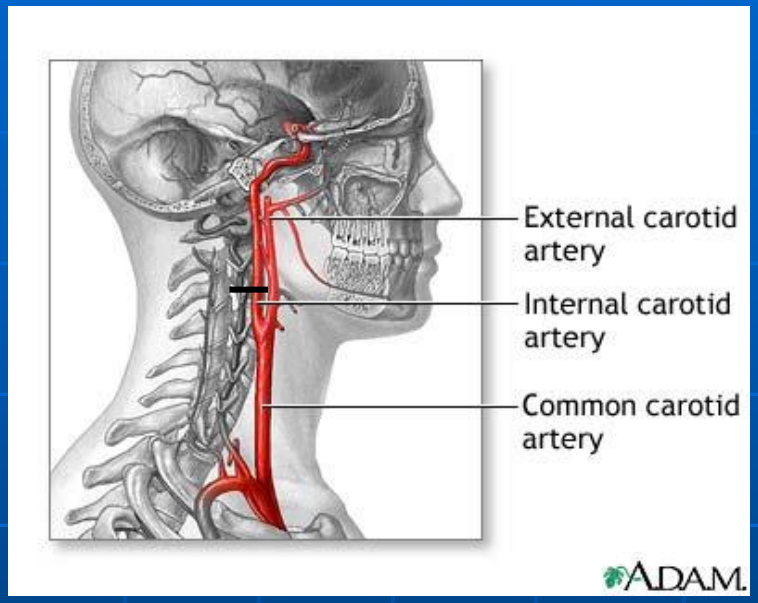




Internal Carotid Artery Clamping

Significant changes in brain oxygenation and Hemodynamics





Conclusions

- Brain vascular response to hypoxia with and without partial scalp ischemia.
- Clamping of external and internal carotids during neurovascular surgery

Q. Does the FD-NIRS and multidistance approach probe the brain?

A. By measuring light simultaneously at multiple distances we reduce the contribution of the superficial layer. Optical properties of the superficial layer have no influence on time-of-flight.

Q. Which are the appropriate source-detector distances?

A. Light collected at 2-4 cm travels deeper into tissue and reaches the surface of the brain.

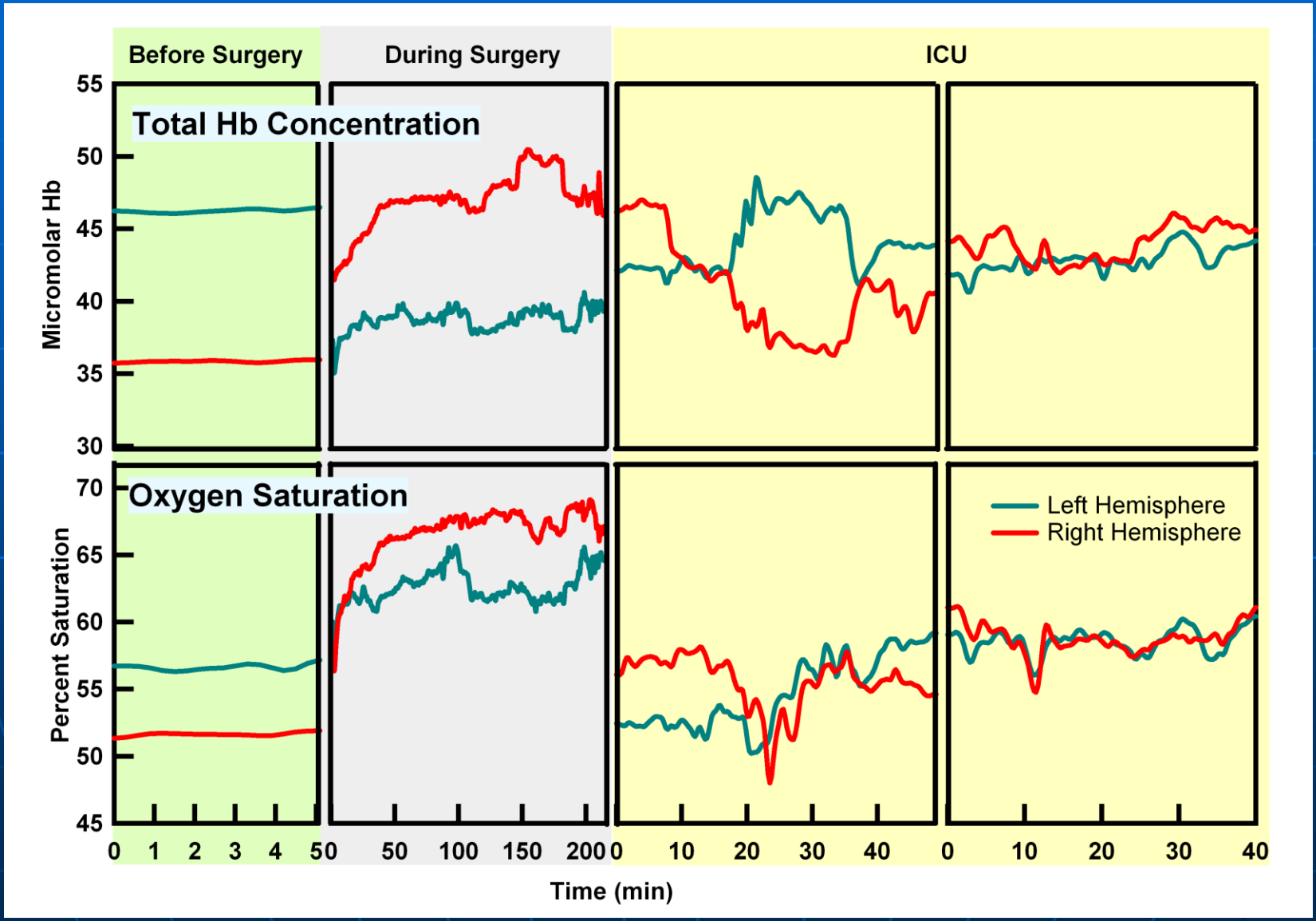
Q. Is our method working?

A. By looking at the details of brain hemodynamics during ischemia we differentiated spatial and temporal hemodynamic changes in the brain.

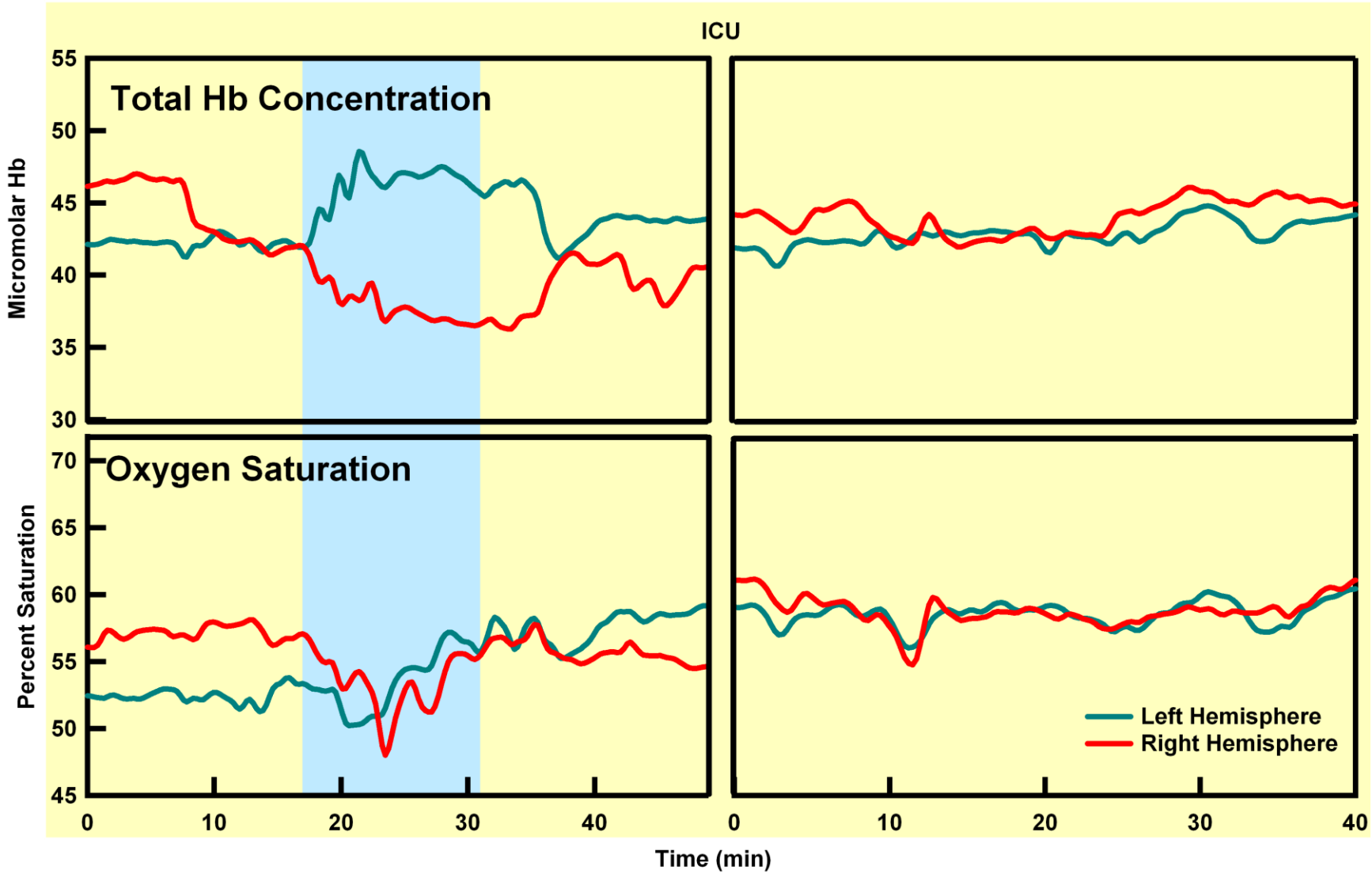
NIRS in Neurosurgery and ICU Post-Operative monitoring

University of Illinois at Chicago Medical Center
Chicago, Illinois

Overall Trace



Monitoring of Brain Oxygenation and Hemodynamics after Surgery



Near-Infrared Brain Oximetry in Obstructive Sleep Apnea Syndrome

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Urbana, Illinois

University of Illinois at Chicago Medical Center
Center of Sleep and Ventilatory Disorders

Sleep apnea. The cessation of airflow through the nose and mouth during sleep that lasts for more than 10 seconds.

Sleep apnea syndrome (SAS). At least 30 apneic episodes observed during a 7-hour sleep period.

SAS types:
1. Obstructive (OSAS)
2. Central
3. Mixed

- 24% of males and 9% of females have 5 or more apneas per hour
- 12% of men and 5% of women present more severe forms (more than 15 apneas per hour)
- OSAS in middle age adults has been identified in approximately 4% of men and 2% in women
- In elderly estimates range from 28% to 67% in men and 20% to 54% in women

Sleep apnea: Risks

- Social and professional impairment
- Traffic and work accidents
- Cardiovascular/pulmonary complications
  a. Systemic hypertension
  b. Pulmonary hypertension
  c. Cardiac arrhythmias
  d. Ischemic heart disease
  e. Alteration of the vascular wall
- Cerebrovascular complications
  a. Neuropsychological dysfunction
  b. Cognitive deficits
  c. Transient ischemic attacks
  d. Strokes
- Death

POLYSOMNOGRAPHY (sleep study)

Monitoring of:

- Snoring
- Respiratory effort
- Naso-oral airflow

Recordings of:

- Electrocardiogram (EKG)
- Electroencephalogram (EEG)
- Bilateral electro-oculogram (EOG)
- Bilateral anterior tibialis Electromyogram (EMG)
- Submental electromyogram (EMG)
- Arterial oximetry

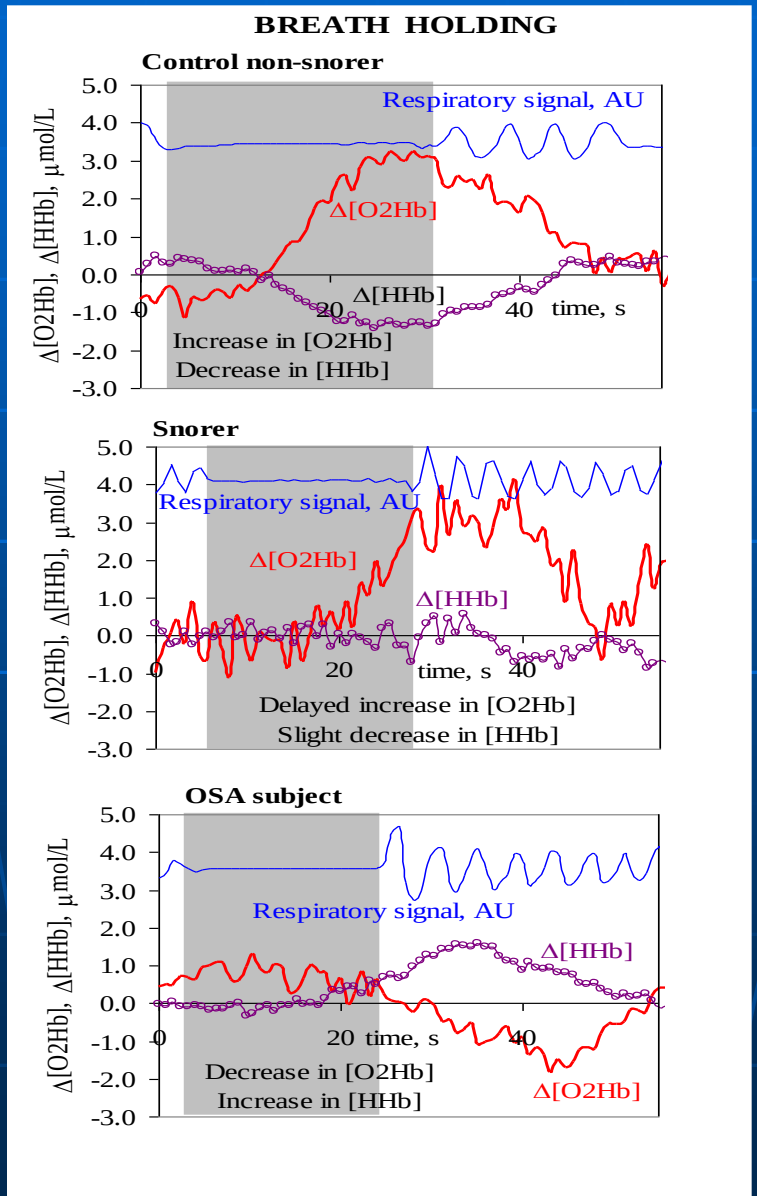
But……it does not provide the clinician with information on **cerebral oxygenation and hemodynamics**, which are important parameters one wishes to determine.

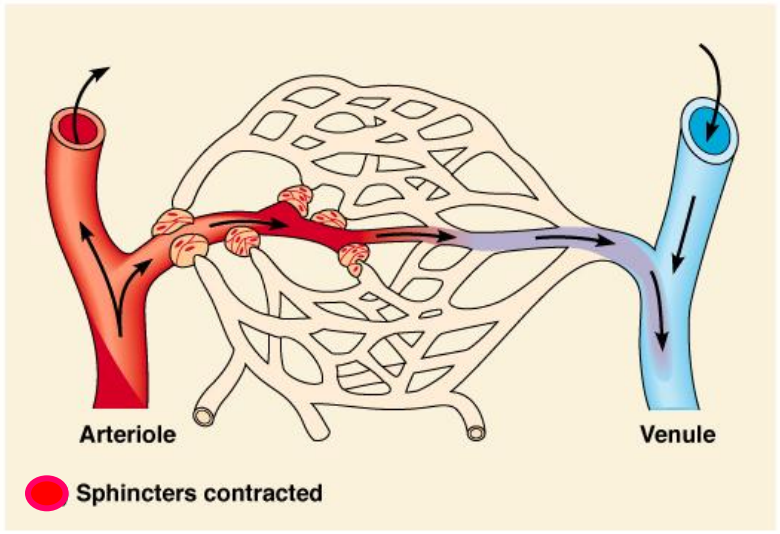
Measurement protocol

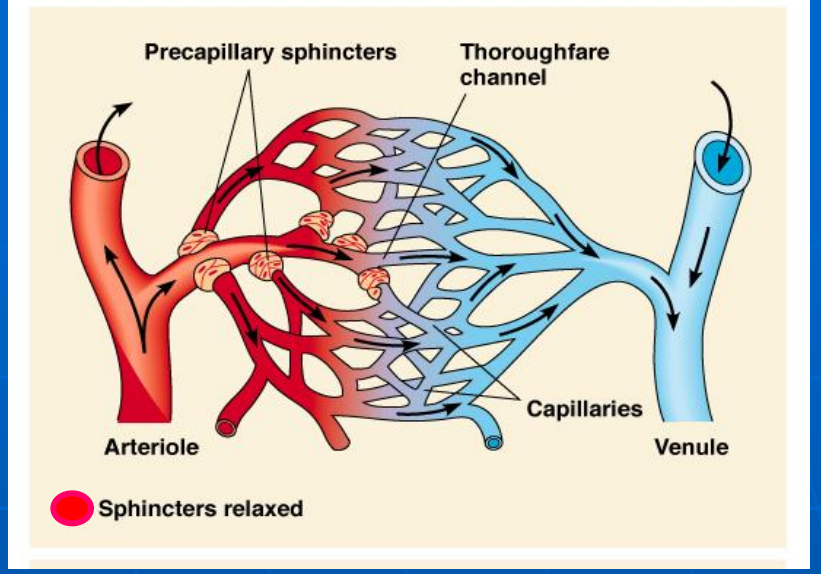
- Breath holding exercises
  - 3-4 min baseline
  - breath holding at FRC with resumption of breathing (3-5 times)
  - 5-10 min baseline recovery
  - Repetition of breath holding and resumption of breathing (3-5 times)

- NIRS measurements during sleep

Changes in cerebral hemodynamics with respect to baseline values







- Capillaries are the ***"heart"*** of the circulatory system, all the action is in the capillaries, and all other blood vessels merely assist them.

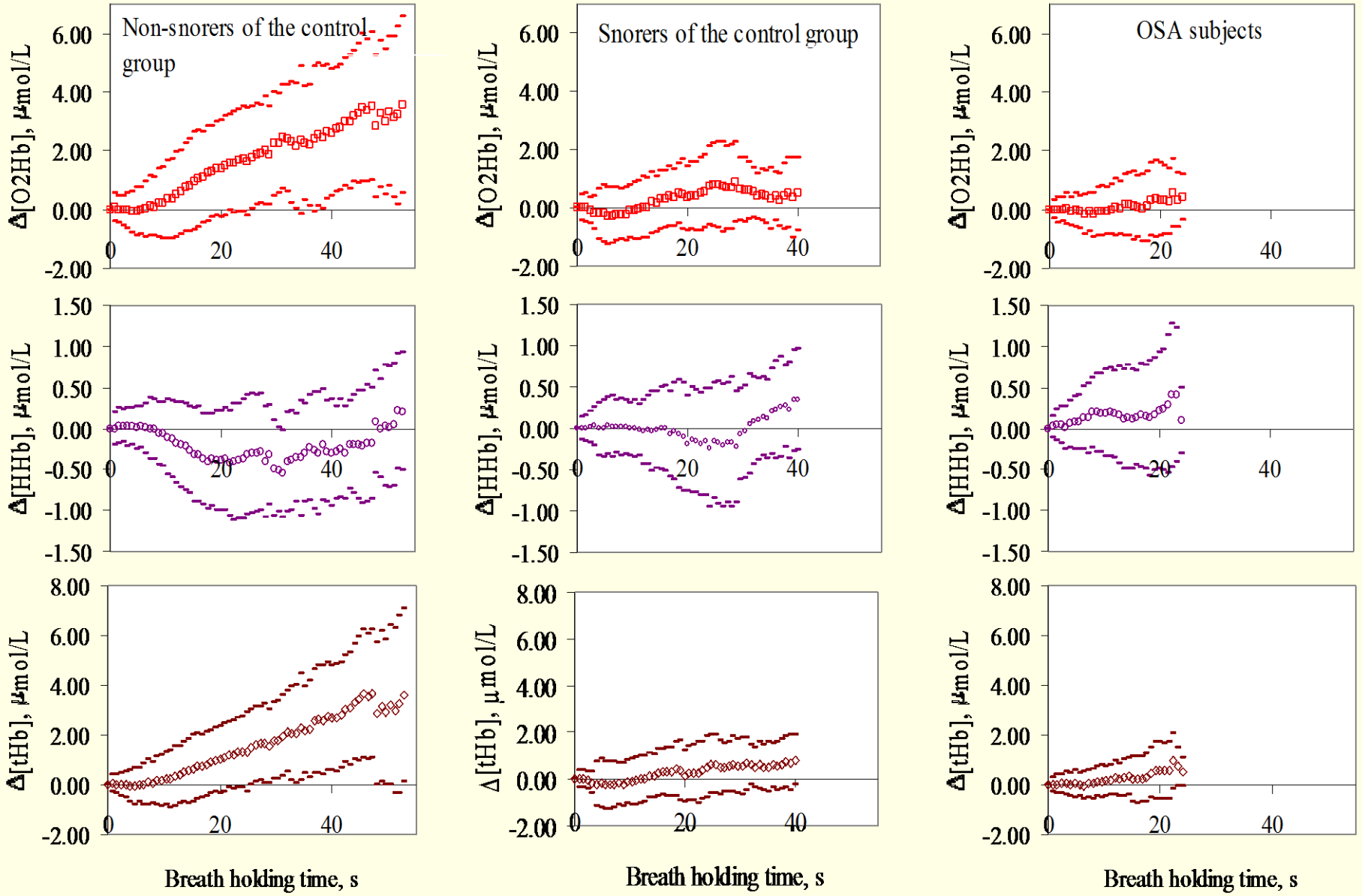
- The blood flow across the capillary bed is regulated by a ***sphincter muscle*** on the ***arteriole*** side. Whenever there is little need to supply blood to a given capillary bed, the sphincter closes and blood bypasses the capillary bed via an ***arterio-venal shunt***.

- The cerebrovascular response to ***hypoxia*** (decreased O2) and ***hypercapnia*** (increased CO2) is vasodilation and opening of the capillary bed.

12 subjects (38±10 years)
72 breath holdings
(30 ±19 s)

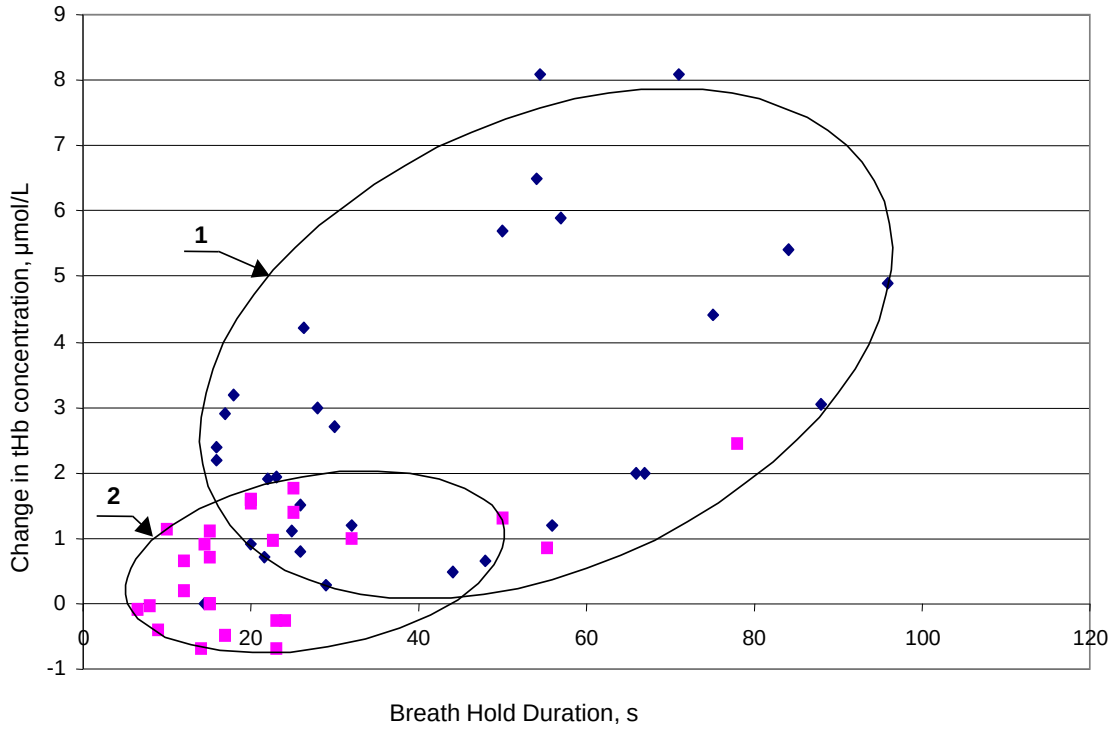
9 subjects (37±16 years)
52 breath holdings
(25 ±11 s)

8 subjects (49±16 years)
58 breath holdings
(18 ±7 s)

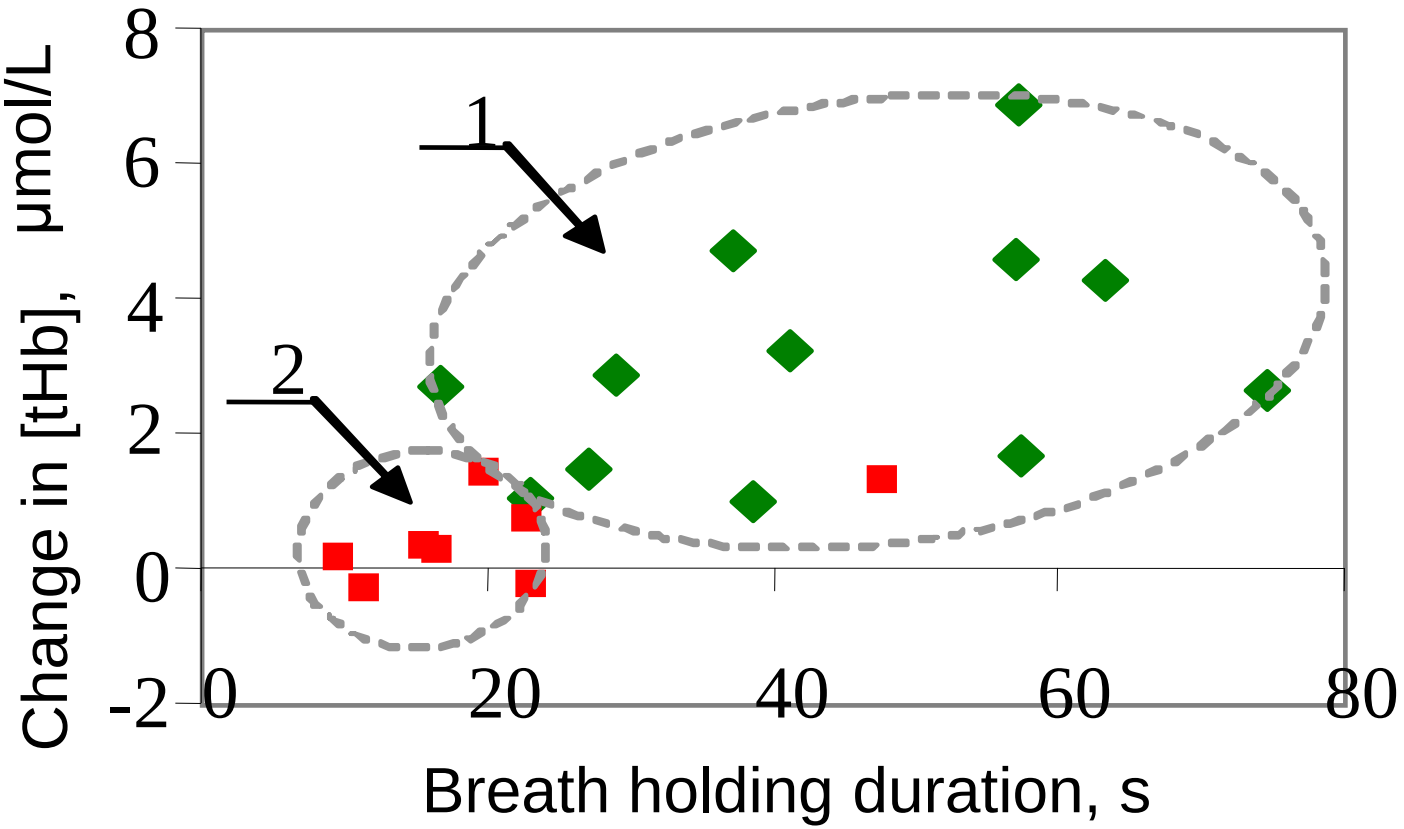


Changes in total hemoglobin concentration during breath holding

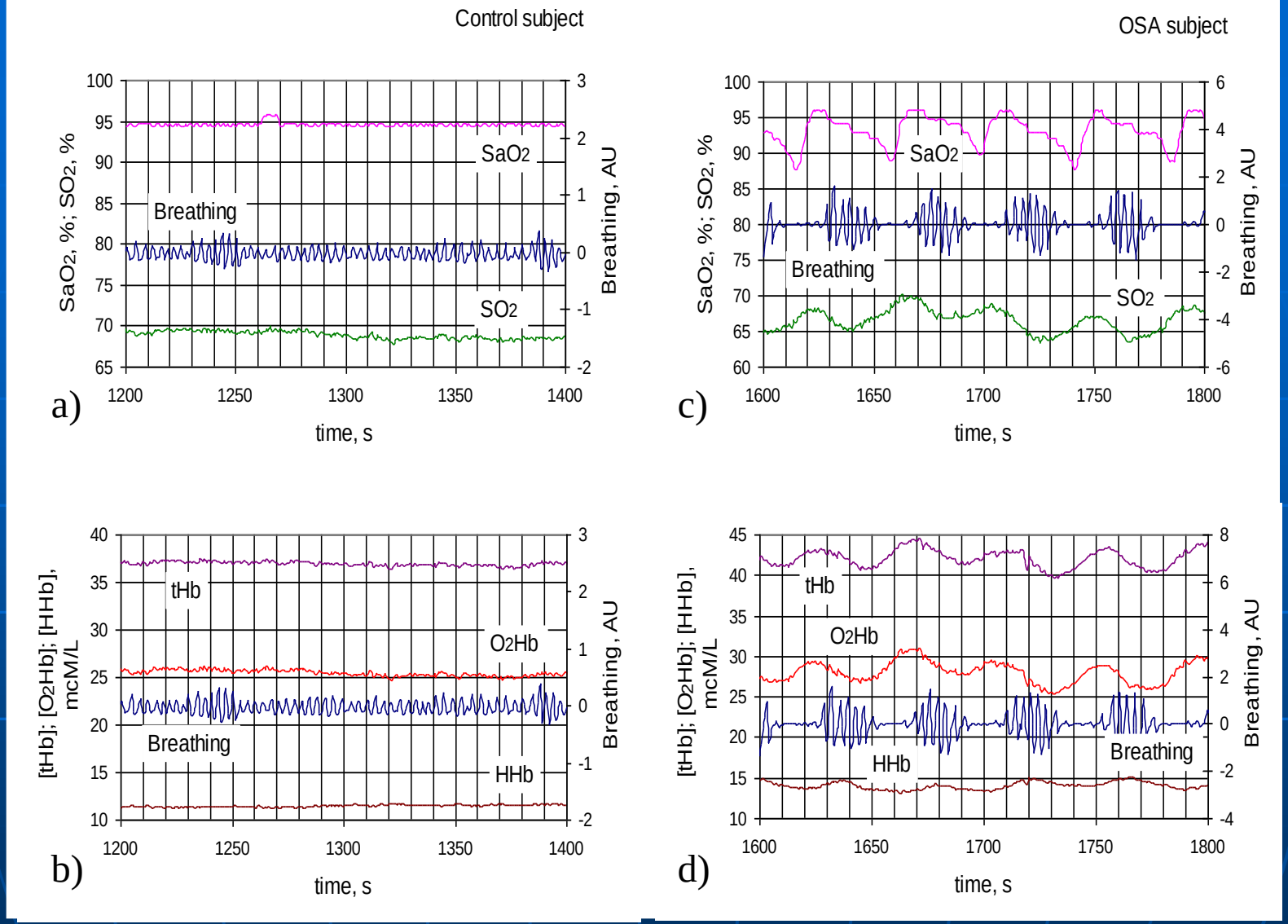
Subjects (matched in number, age and sex)	Duration of the breath holding, s	Change in tHb concentration, μmol/L
	dt	d[tHb]
Controls (8 subjects/ 8sessions/ 31 breath holds)	42.0±24.1	2.9±2.3
OSAS (8 subjects/ 8sessions/ 26 breath holds)	22.3±15.8	0.6±0.9



1 - area of tHb changes observed for control subjects
2 - area of tHb changes observed for OSAS subjects



Changes in brain tissue total hemoglobin concentration (changes in cerebral blood volume)
1 - area of changes in control non-snorers
2 - area of changes in OSA sufferers

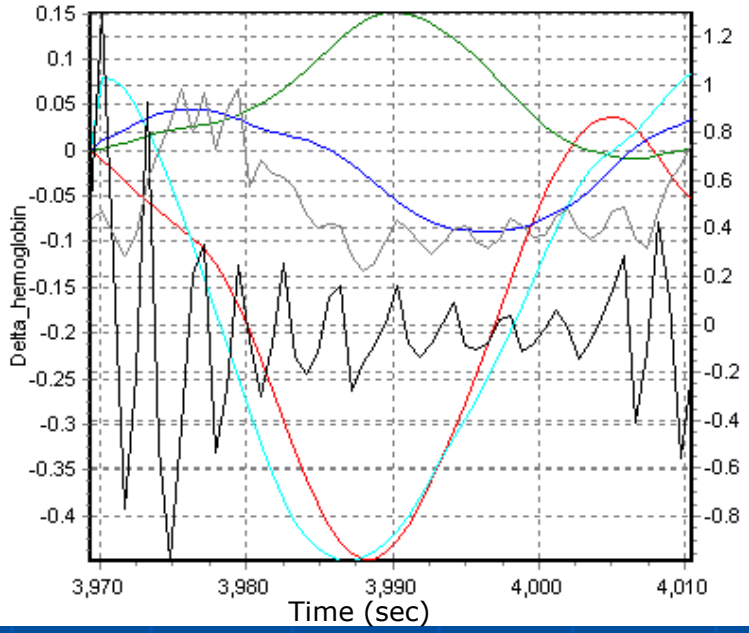


Changes in brain hemodynamics and tissue oxygenation during sleep

(a,b) control subject, (c,d) OSA subject

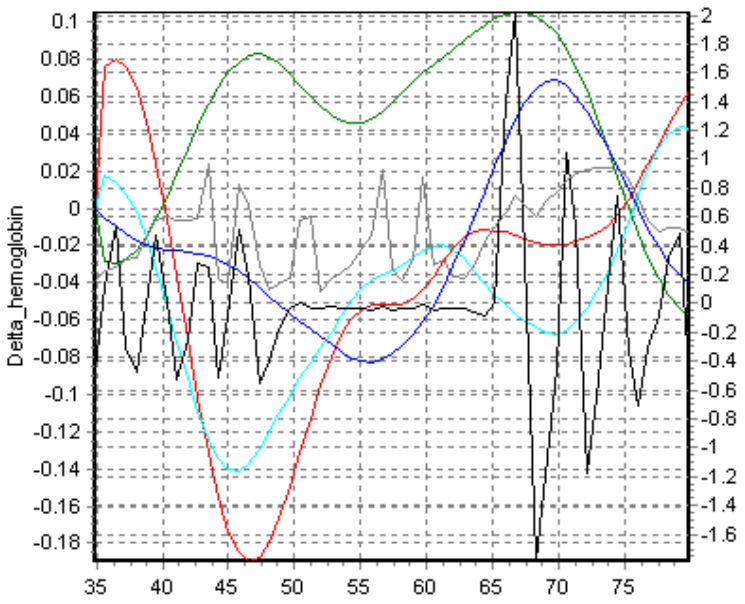
Arterial blood oxygen saturation (SaO2) is measured via pulse oximetry.
Breathing is monitored via a strain gauge around the chest.
Brain tissue oxygenation (SO2) and tissue hemoglobin oxygen saturation are measured by NIRS

Sleep Apnea



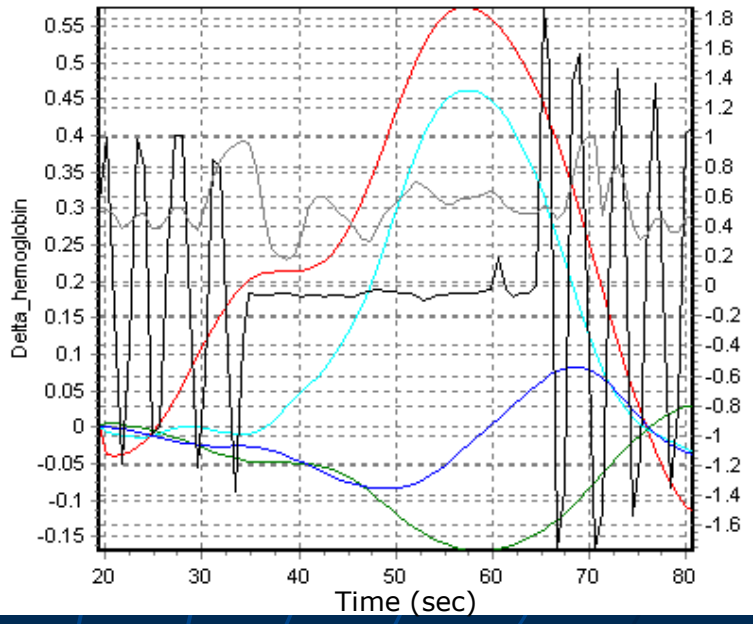
OSA sufferer

Breath holding



Hemodynamic responses to hypoxia

Control



Right Frontal Lobe: **Oxy-Hb (Red)**

Deoxy-Hb (Blue)

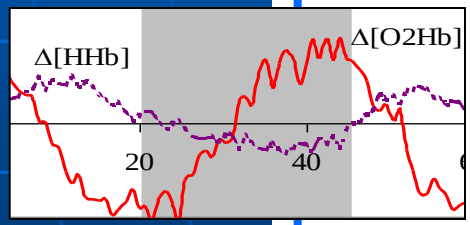
Left Frontal Lobe: **Oxy-Hb (Light Blue)**

Deoxy-Hb (Green)

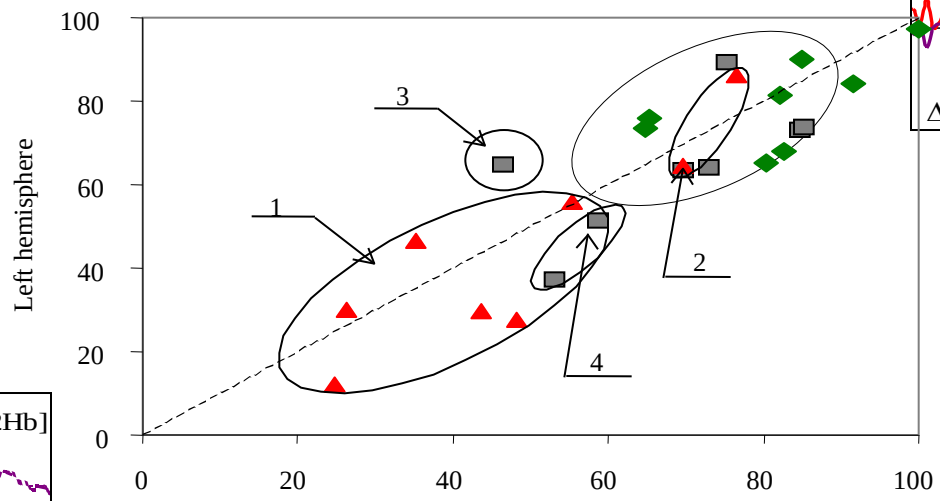
Breathing (Black)

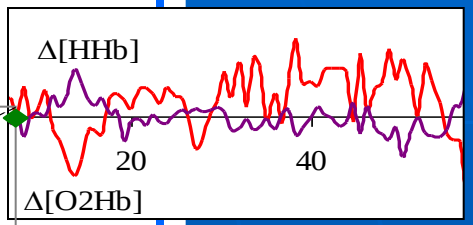
Pulse (Gray)

Characterization of the subjects based on changes in [O_2Hb] and [HHb] due to breathing during sleep



Probability of opposite phase changes in [O2Hb] and [HHb] due to respiration sleep, %



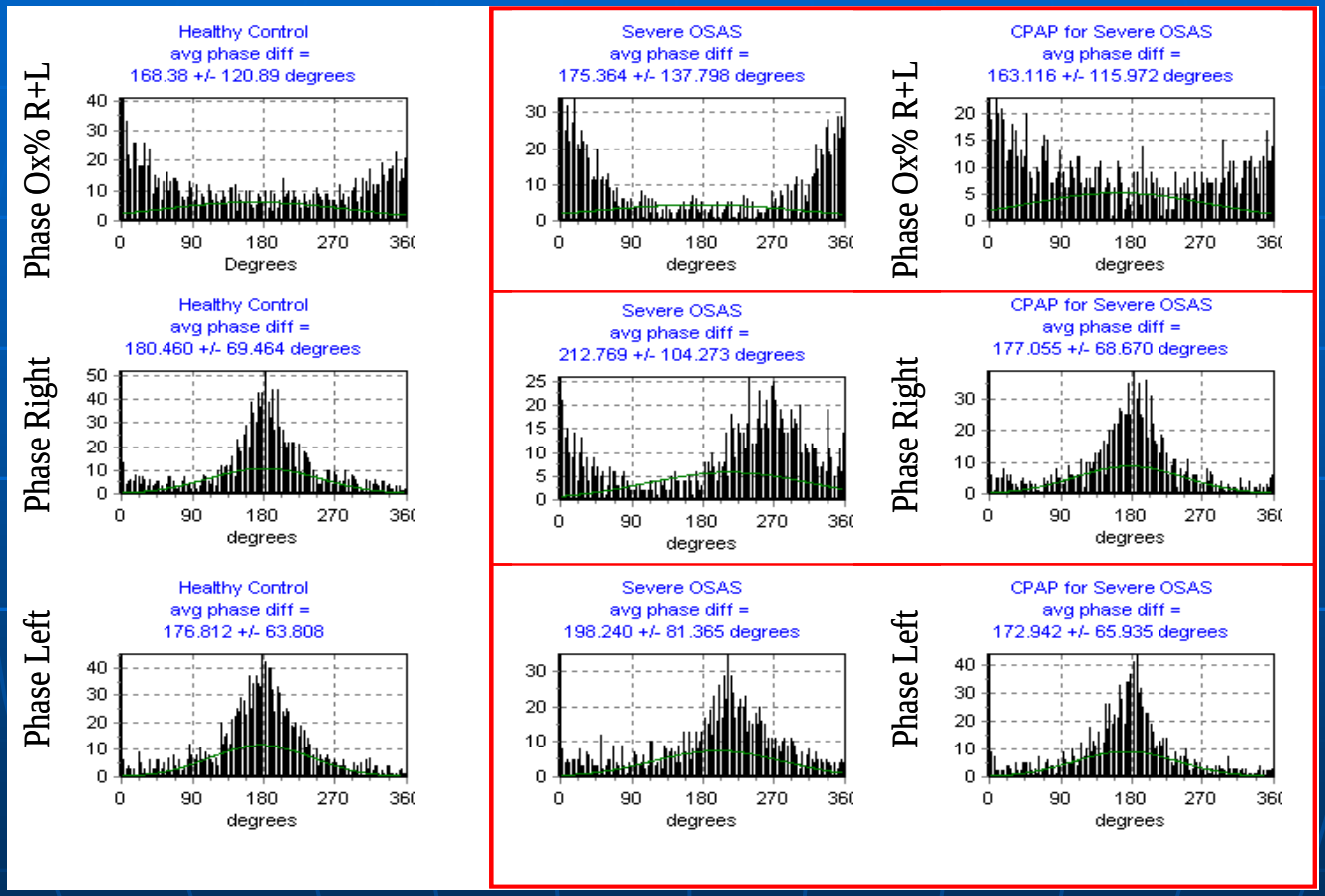


1 - severe OSA subjects;
2 - youngest OSA subjects (29 & 44 years old)
3 - snorer with a family history of OSA ;
4 - oldest snorer (73 years old);

We track the intra-hemispheric temporal correlations to observe anti-correlation or anti-phase behavior with respect to the changes in oxy- and deoxy-Hb, which is displayed as an angle of 180 degrees.

Analysis Schemes:

The Hilbert Transform provides two types of temporal information: (1) we can track the correlations in time and (2) we can analyze all the points in time as a histogram. The figures show the histograms of the inter-hemispheric oxygenation (Ox%)



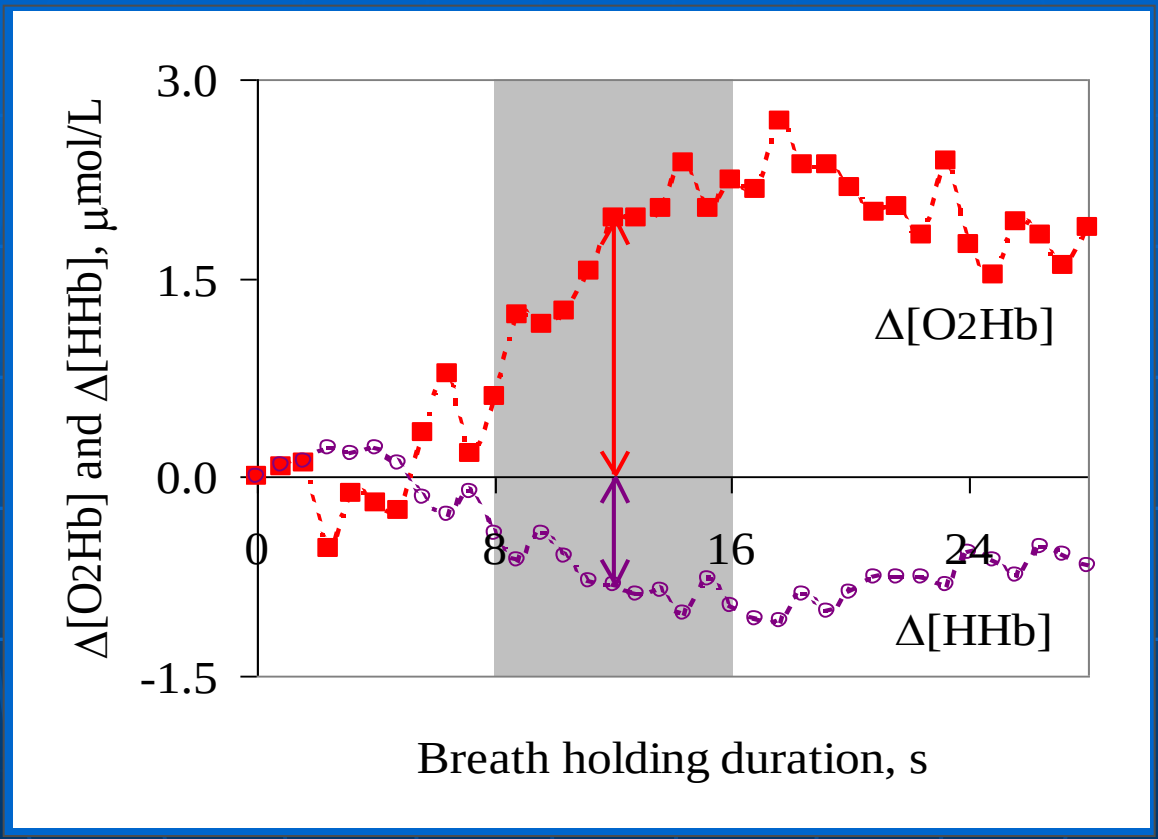
Healthy Control: six hours of sleep in histogram [column 1]
OSAS: three hours of sleep with multiple apneic events [column 2, red box]
CPAP: three hours of sleep in OSAS subject with CPAP [column 3, red box]
(Split PSG study: OSAS subject is diagnosed and fitted with CPAP for apneic event reduction therapy.)

Conclusion

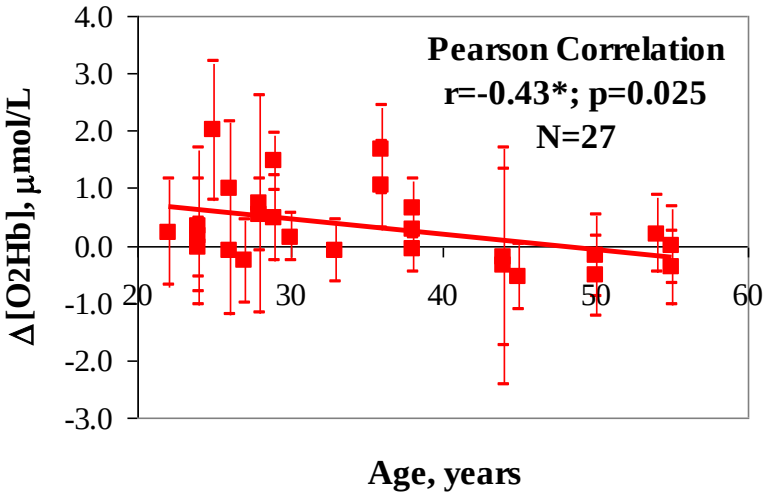
- NIRS provides non-invasive, transcranial, real-time measurements of cerebral oxygenation and hemo-dynamics.
- NIRS gives direct information on cerebrovascular autoregulation.
- NIRS may provide a cost-effective screening for cerebrovascular morbidity in OSAS sufferers.
- NIRS may be associated with the standard overnight polysomnography to monitor brain vascular responsiveness to hypoxia in OSAS.

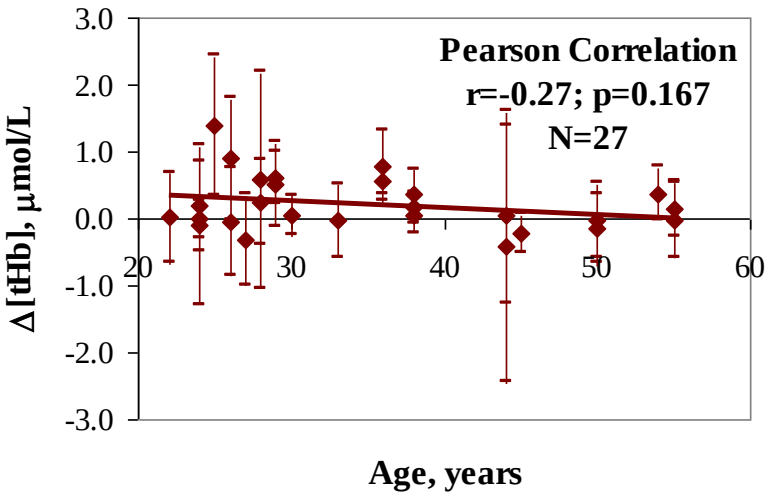
Age correlated changes in cerebral hemodynamics assessed by near-infrared spectroscopy

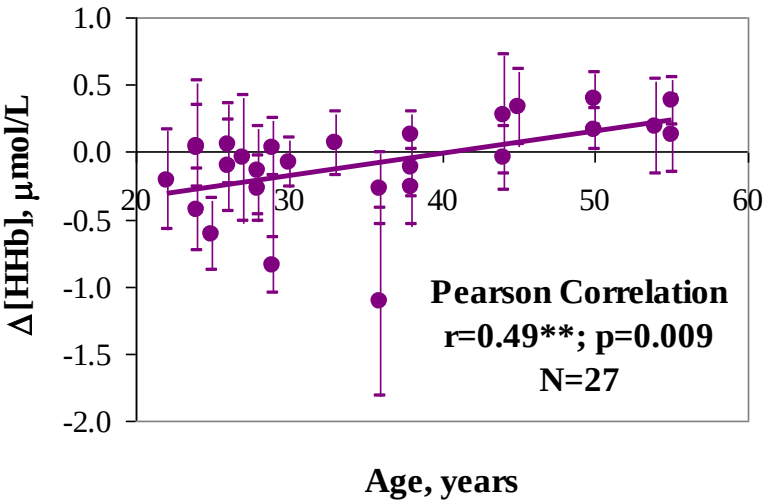
Changes in oxy- and deoxy-hemoglobin concentrations assessed in a control non-snorer during breath holding

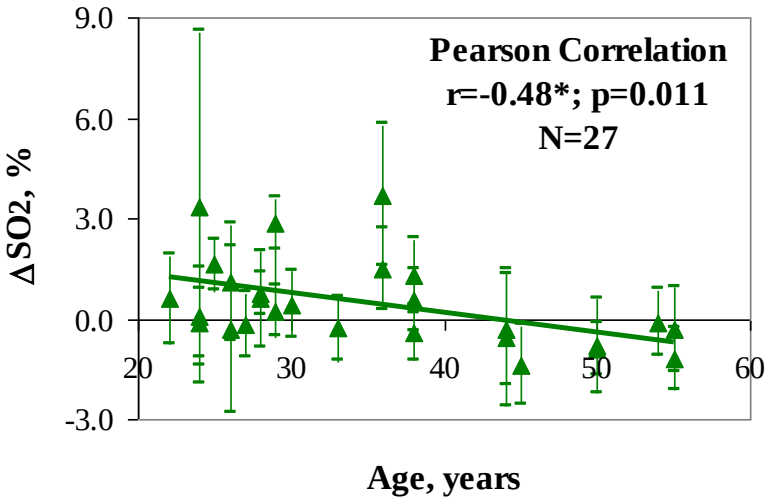


Analyzed changes in cerebral hemodynamic parameters on the 12th second of breath holding and mean changes during the 8th – 16th seconds (shaded area).









Decreases in $\Delta[O_2Hb]$, $\Delta[tHb]$, and ΔSO_2, and an increase in $\Delta[HHb]$ during hypoxic episodes were observed in older subjects.

NIRS in Attention Deficit Hyperactivity Disorder (ADD/ADHD)

Collaborative Project

University of Illinois at Urbana-Champaign
Laboratory for Fluorescence Dynamics

Carle Clinic, Urbana Illinois
UIUC College of Medicine, Department of Pediatrics

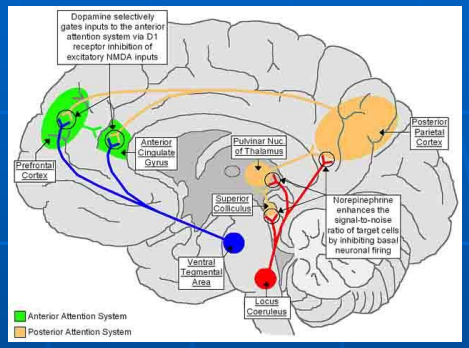
The University of Texas
Southwestern Medical Center at Dallas
Department of Pediatrics

ADHD - Attention Deficit Hyperactivity Disorder

The most common psychiatric developmental disorder in USA

Qualitative Diagnosis

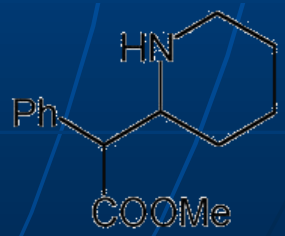
- Hyperactive type: “always on the go”
- Inattentive type: “struggle to stay focus”
- Mixed type: the most common
- Symptoms must be constant and across settings



Hypoperfusion hypothesis

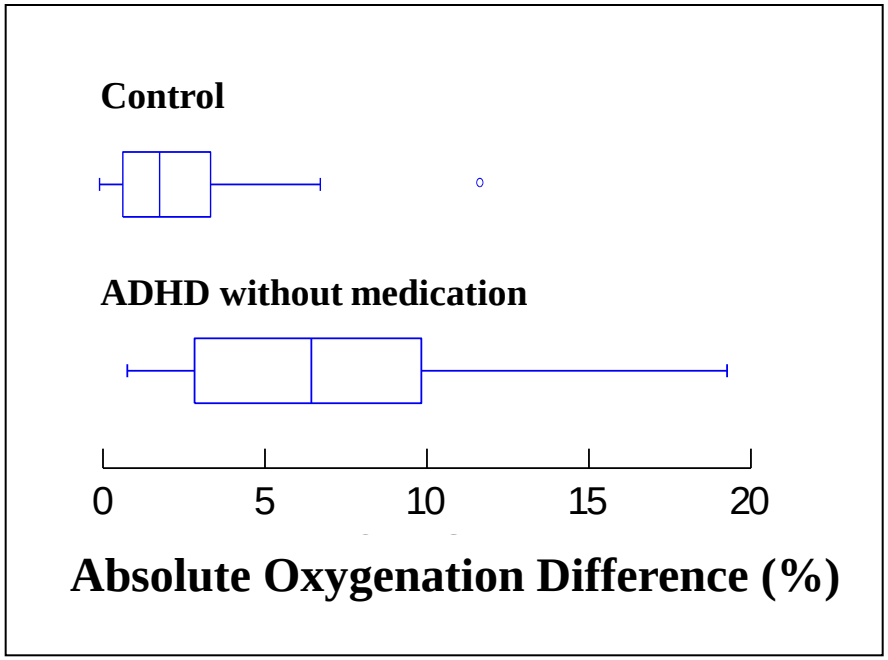
- abnormal distribution of regional Cerebral Blood Flow (**rCBF**)
- frontal lobes, frontal-striatal-cerebellar circuits
- volumetric evaluation: PET, MRI, CT

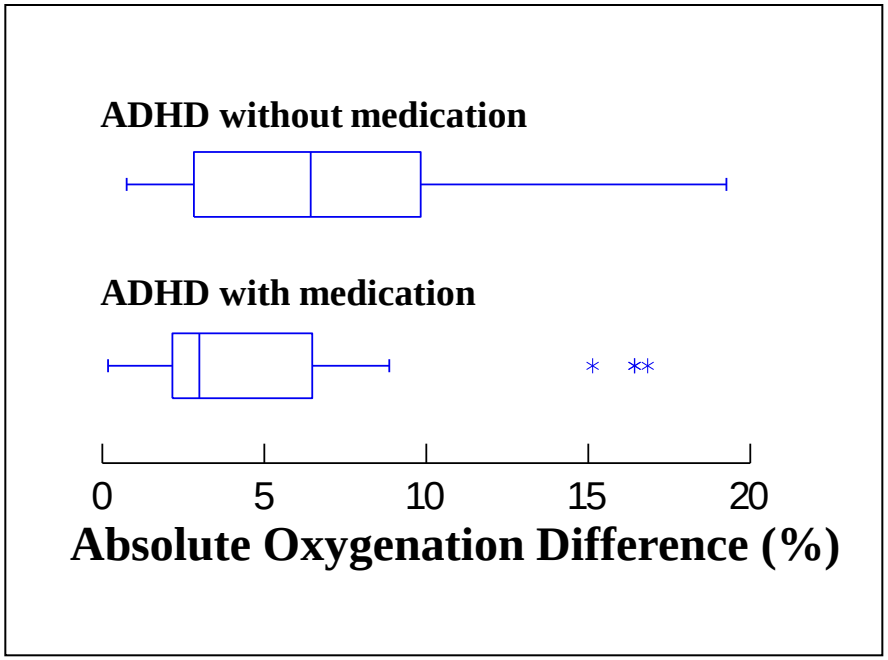
Methylphenidate



- stimulates the release/block of reuptake of extracellular dopamine in the synaptic cleft.
- reduces inattentive, impulsive, and hyperactive symptoms.

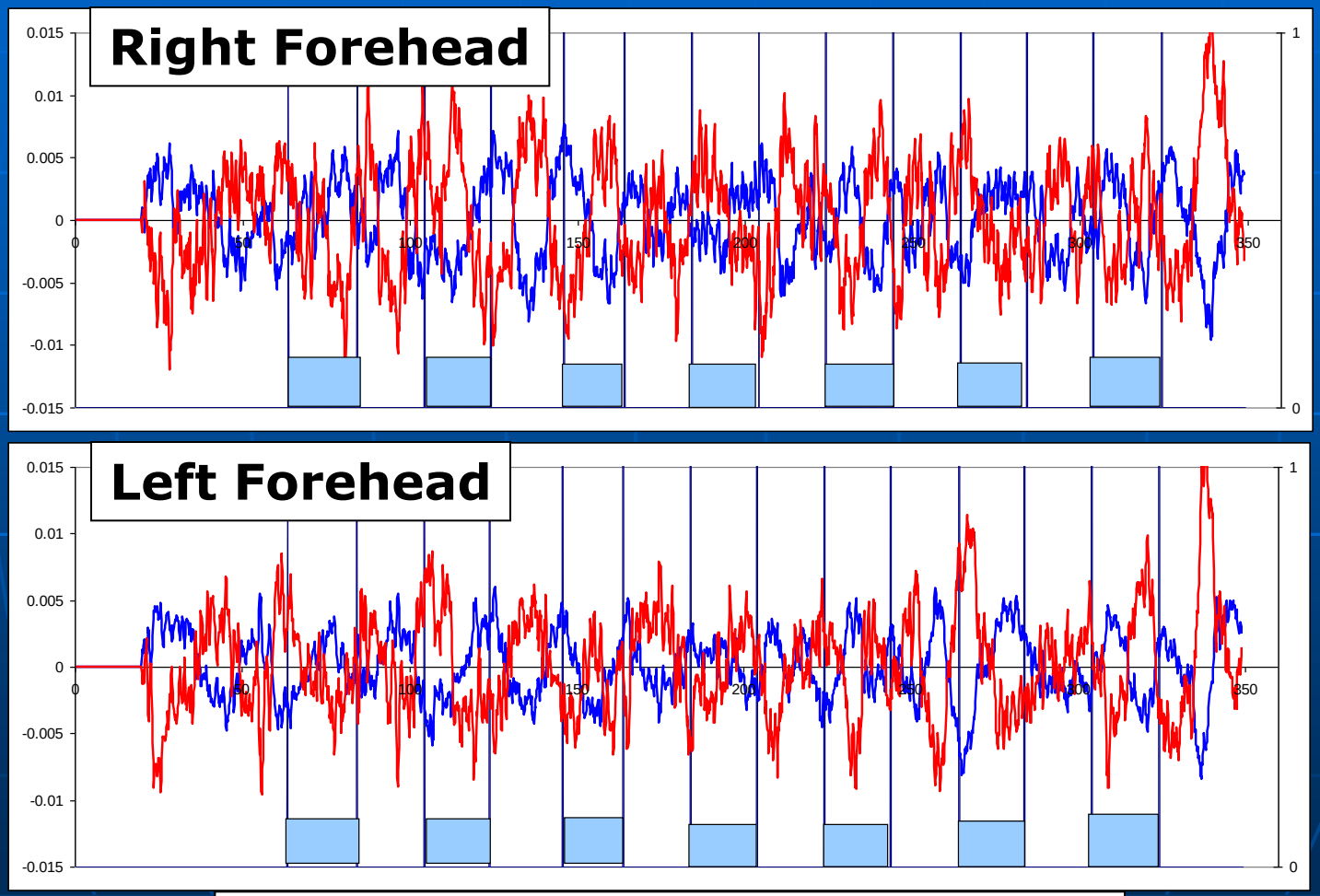
Potential Diagnostic Screening





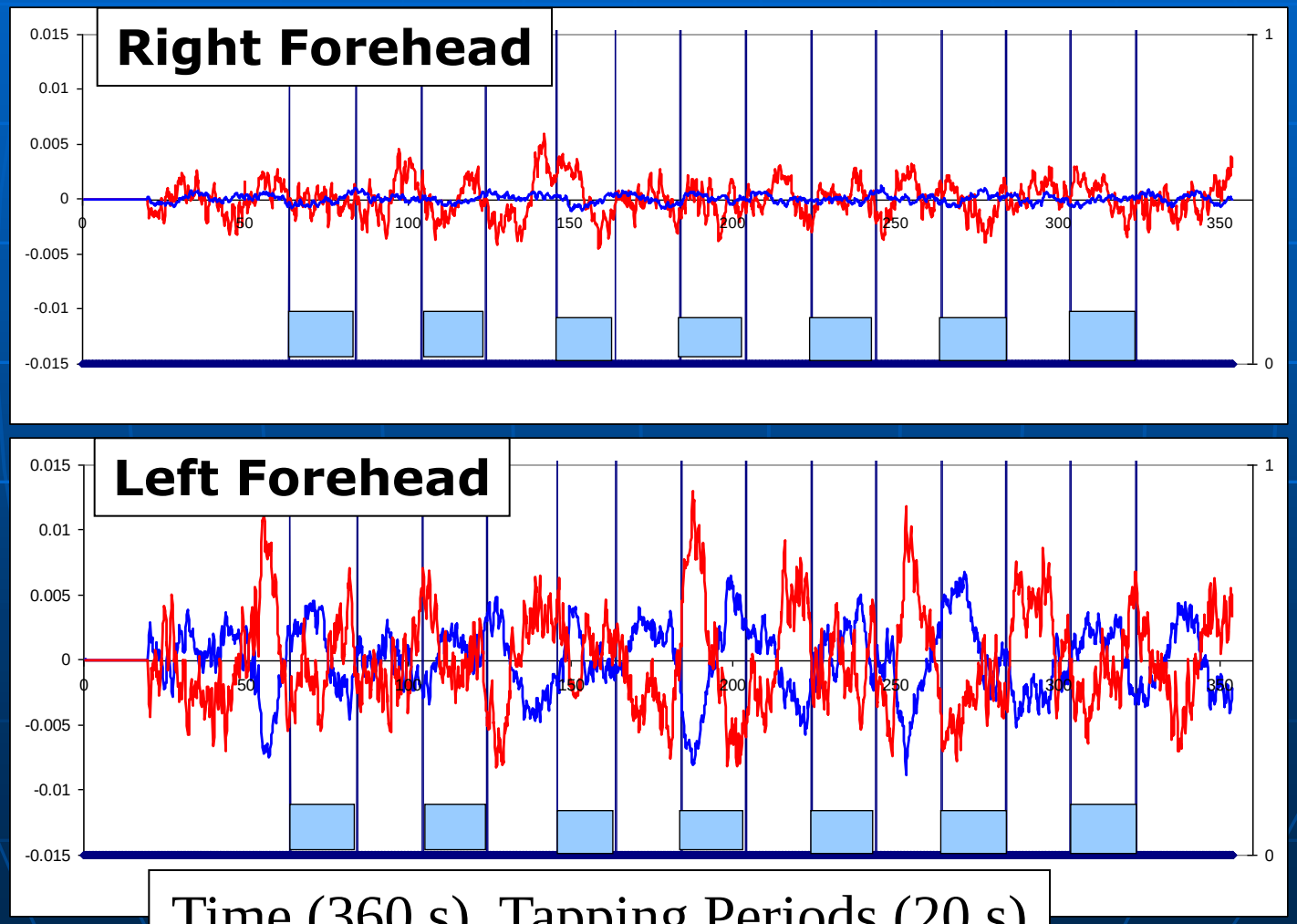
7 years old control child

Tapping exercise, Right hand.



Time (360 s), Tapping Periods (20 s)

7 years old ADHD hyperactive child Tapping exercise, Right hand. Showing regional hypoperfusion?



Final Remarks

- NIRS provides non-invasive, transcranial, real-time measurements of cerebral oxygenation and hemodynamics.
- NIRS can measure absolute values of the concentrations of [HbO2], [HHb], and [tHb] and tissue oxygenation.

- NIRS aims to study specific hemodynamic patterns in ADHD:
  - detect hypoperfusion with functional NIRS.
  - detect brain development anomaly in populations of young children.
  - assess brain segregation in the frontal lobes in ADHD.
  - contribute to ADHD diagnosis and pharmacological treatment.
- More synchronous locations for measurements are needed.

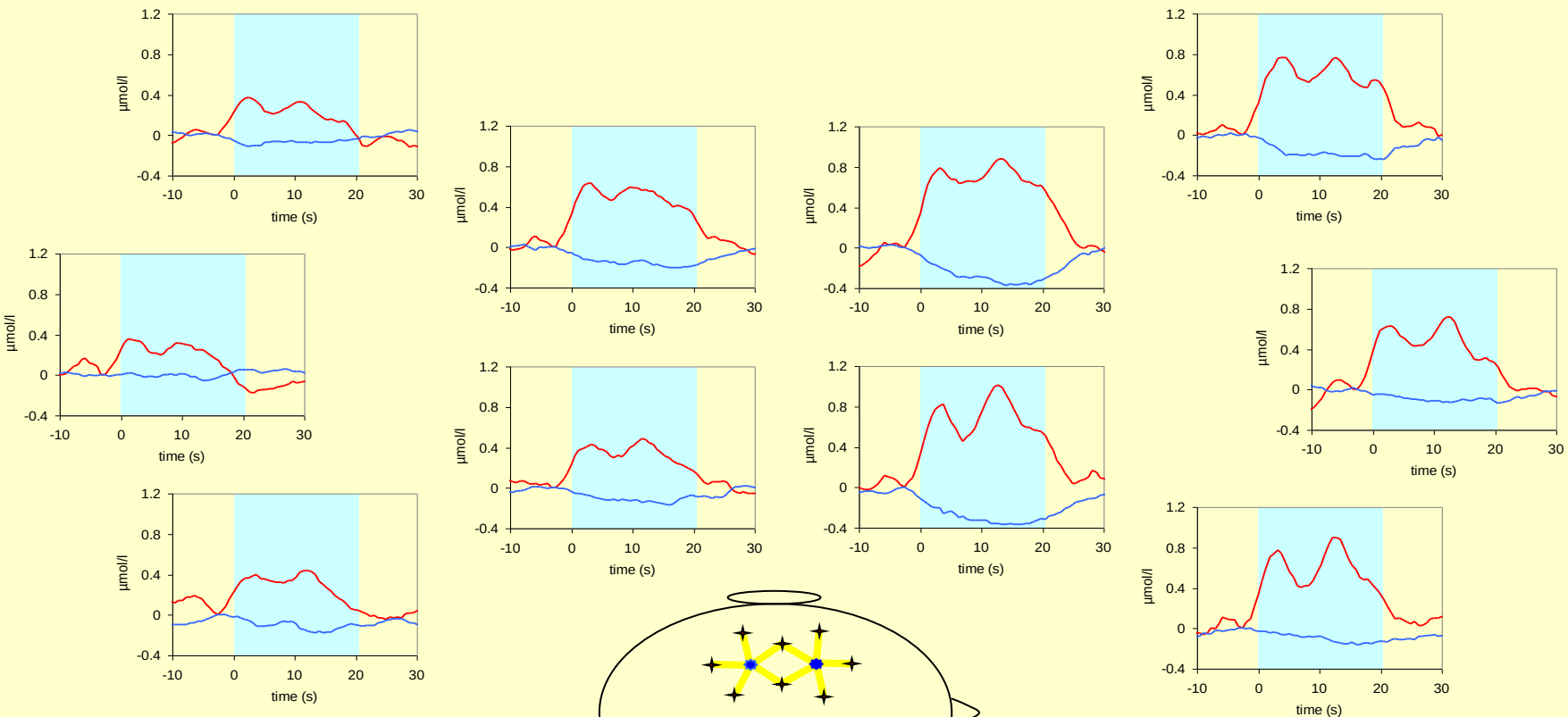
Motor cortex activation

Collaborative project

University of Illinois at Urbana-Champaign
Laboratory for Fluorescence Dynamics

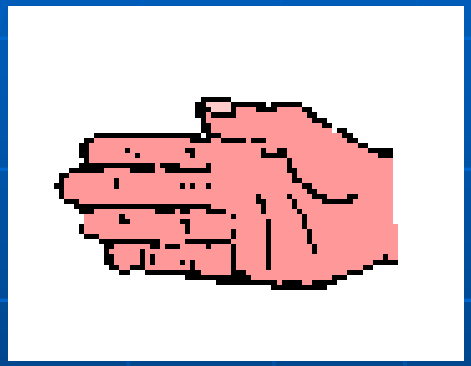
Tufts University, Medford MA
Department of Electrical Engineering and computer Science

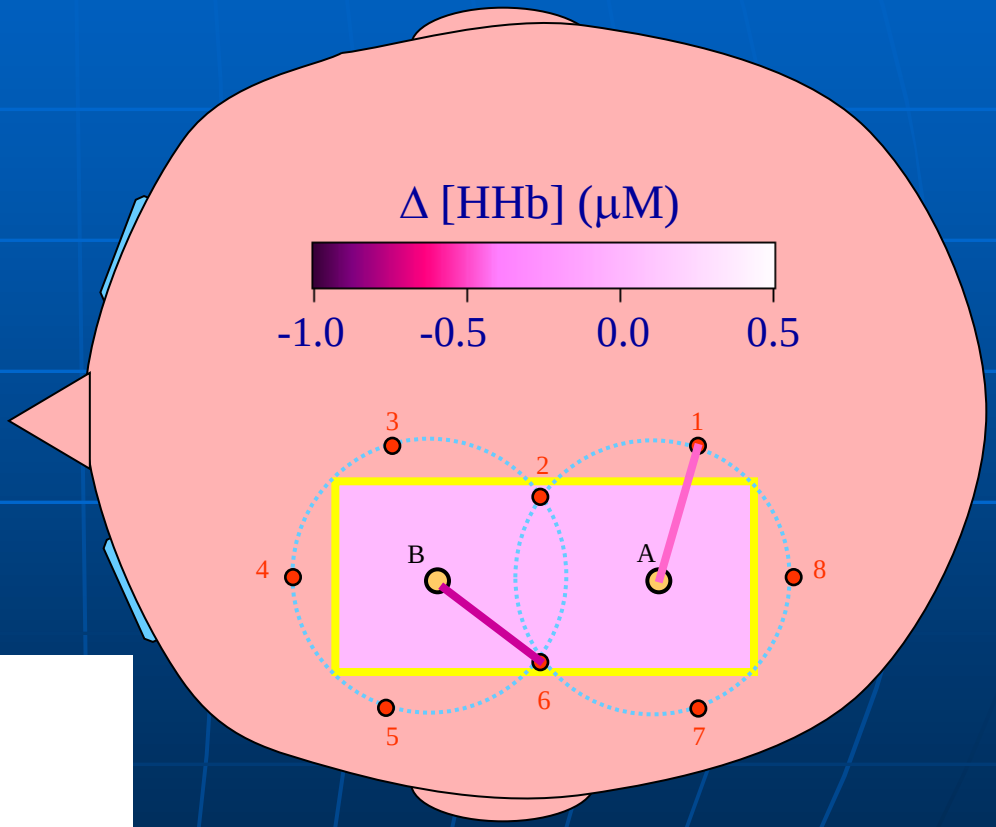
Plots of Source-Detector Pairs by DPF

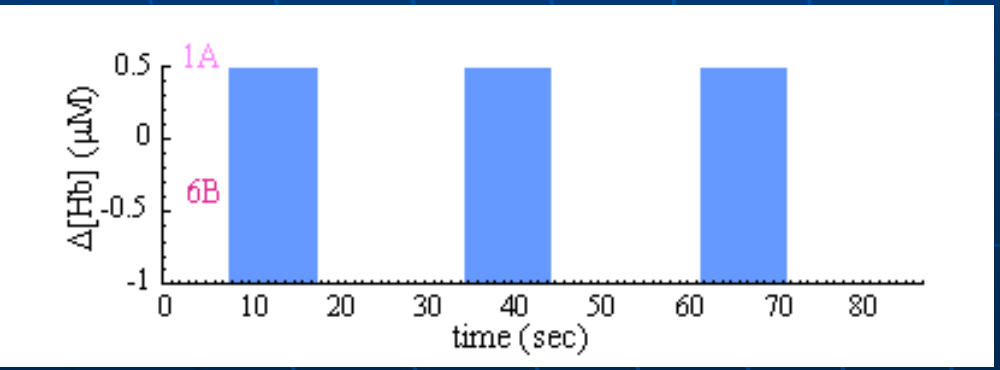


Motor cortex activation

Data acquisition frequency = 1.25Hz

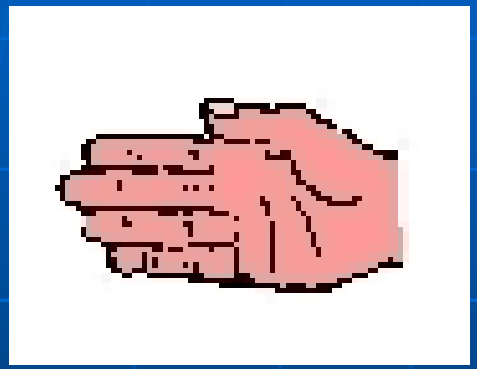


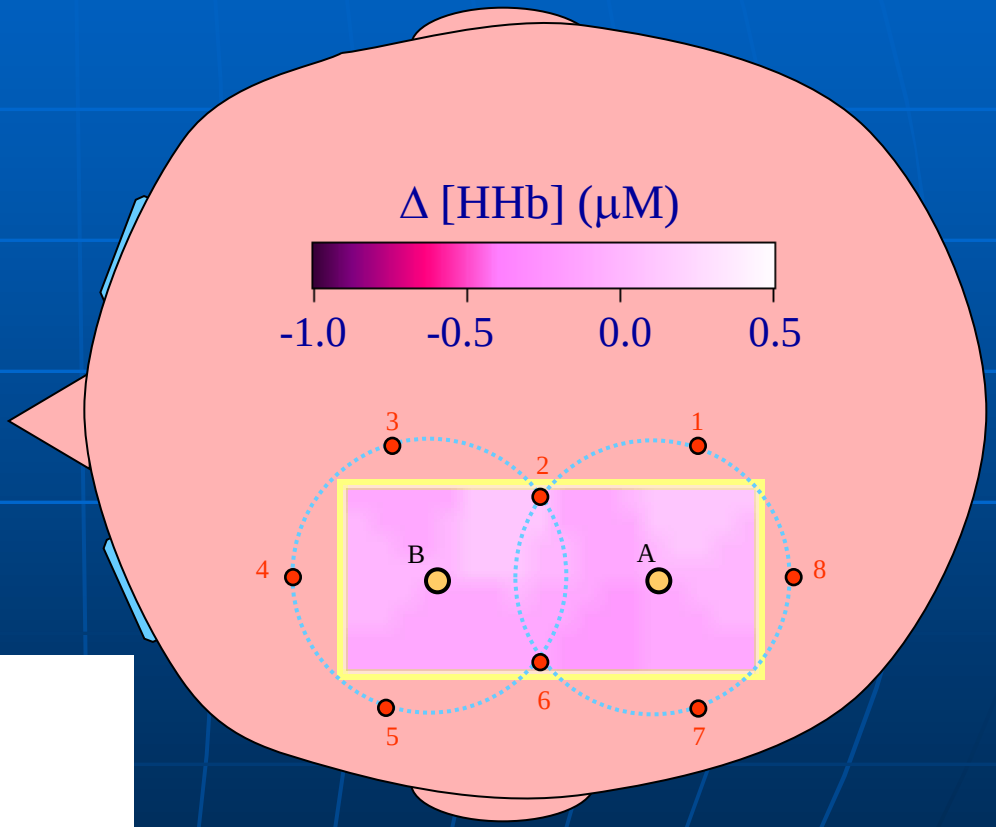


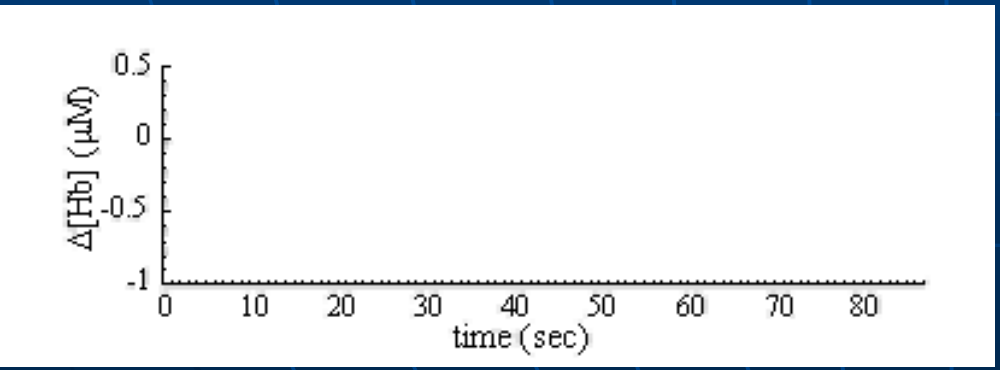


Motor cortex activation

Data acquisition frequency = 1.25Hz







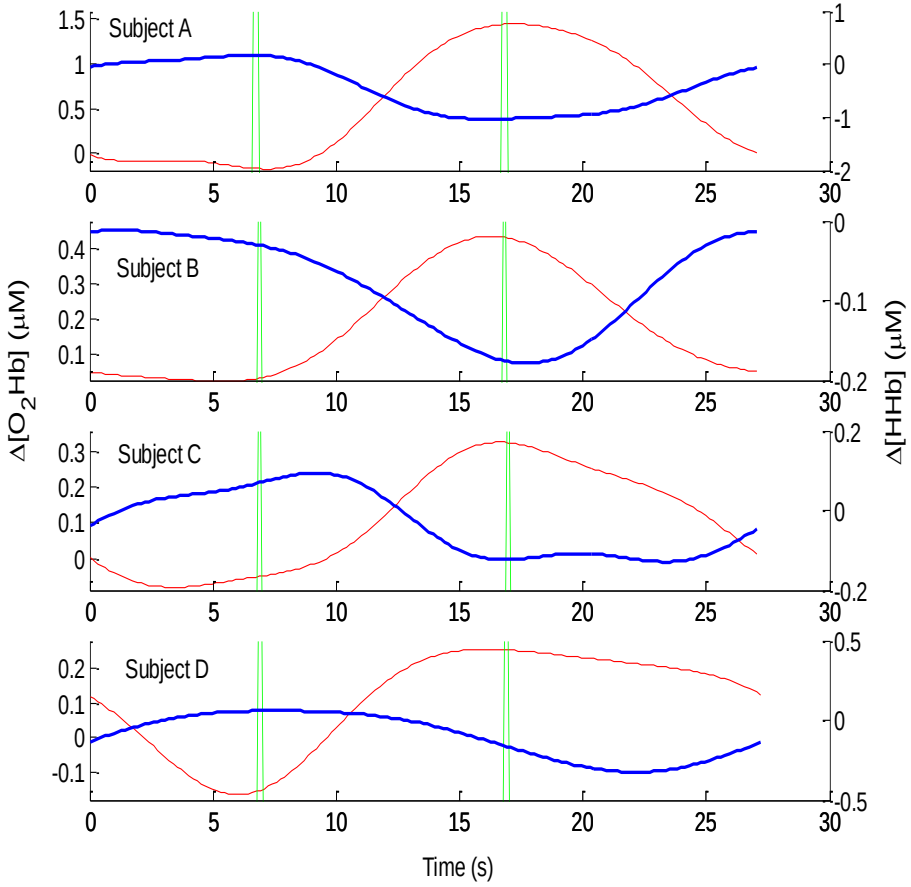
Simultaneous measurement of fMRI and NIRS of brain function

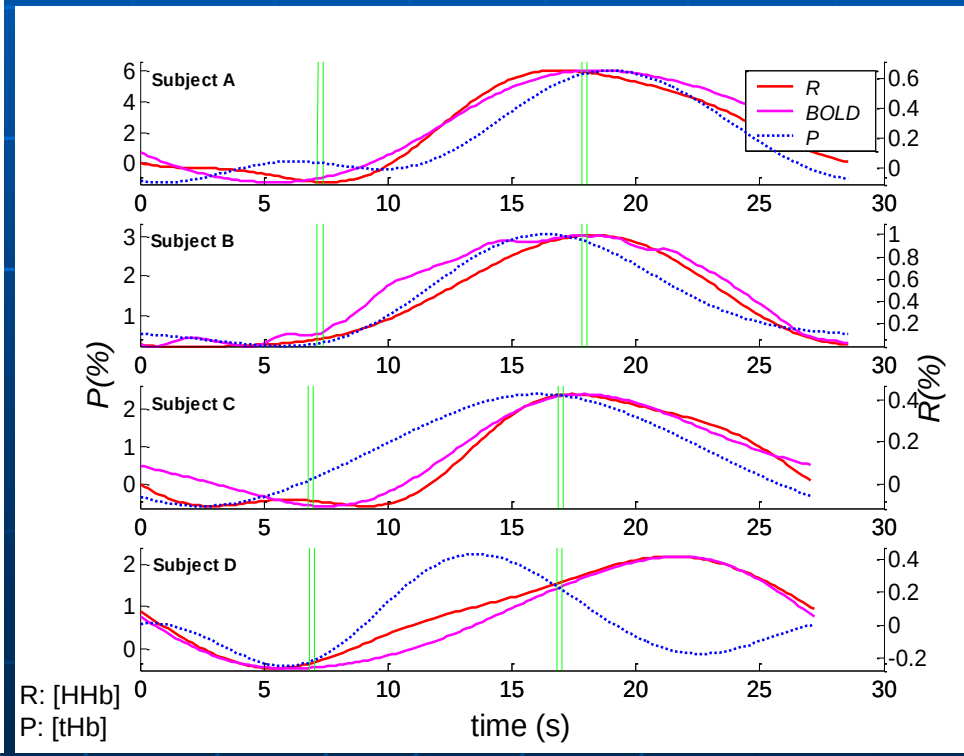
Collaborative Project

University of Illinois at Urbana-Champaign
Laboratory for Fluorescence Dynamics
Beckman Institute

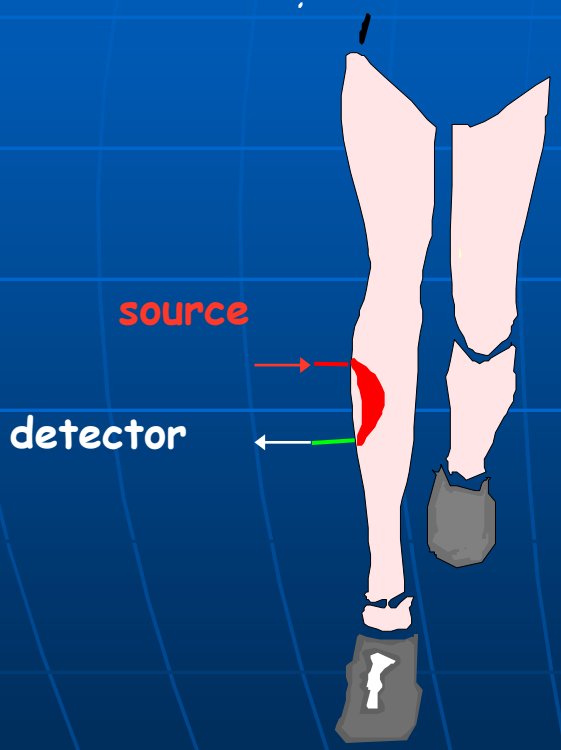
Carle Hospital Foundation, Urbana IL

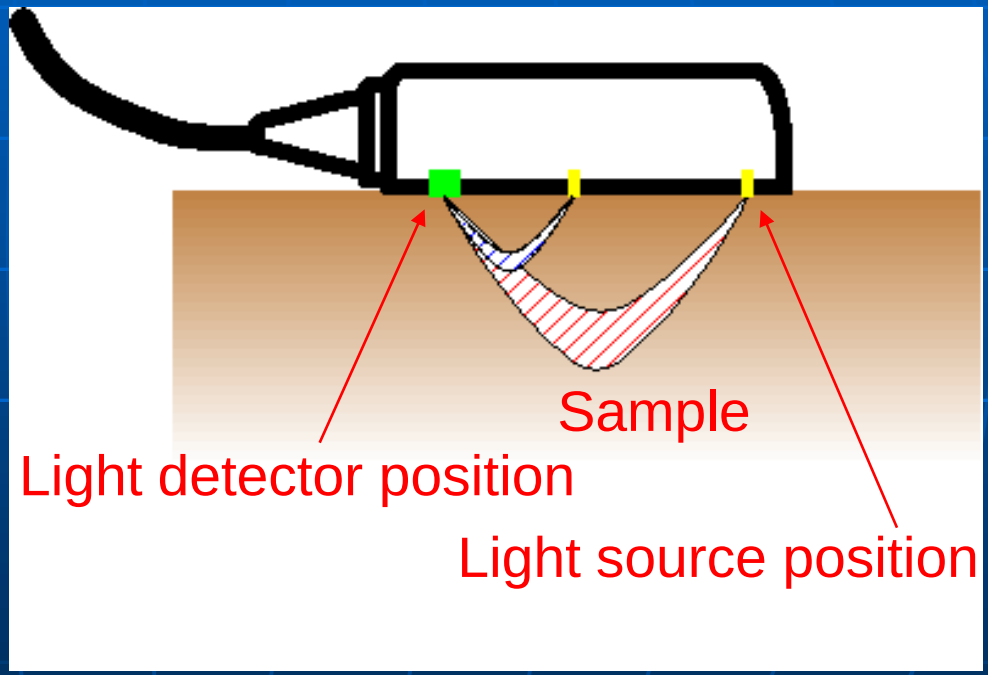
Simultaneous Multi-source Frequency-domain NIRS and BOLD fMRI signals during motor functional activation in humans: Collocation of signals





The Absorption and Scattering of Intensity Modulated NIR Light is Measured in the Tissue Beneath the Sensor





Peripheral Vascular Disease

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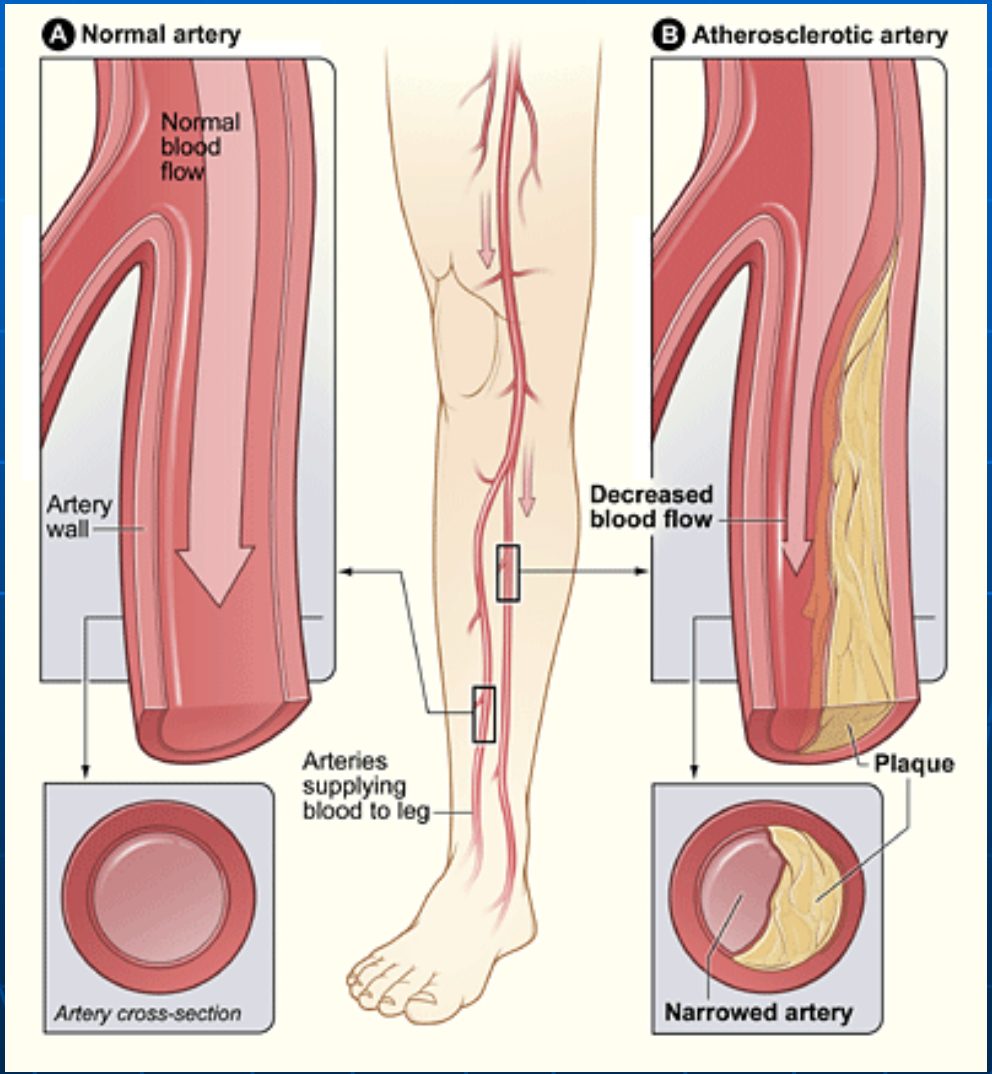
University of Illinois at Urbana-Champaign
Laboratory for Fluorescence Dynamics

UIUC College of Medicine, VA Hospital, Danville, Illinois

The University of Texas
Southwestern Medical Center at Dallas, Department of VA

Policlinico Monteluce, University of Perugia, Italy

- Peripheral Vascular Disease (PVD) is a chronic condition characterized by poor circulation in the extremities



- PVD manifests as insufficient tissue perfusion
- Blocked blood flow can cause pain and numbness. It can result in dangerously low delivery of Nutrients and Oxygen to tissues especially in the foot and lower leg
- Affects 12-14% of General Population and >20% of people over 75
- Over 100,000 Surgical Interventions Per Year
- Early Detection, Monitoring, and Treatment May Improve Quality of Life and Reduce Surgeries

The Human Clinical Trial for PVD Assessment

Patient Groups

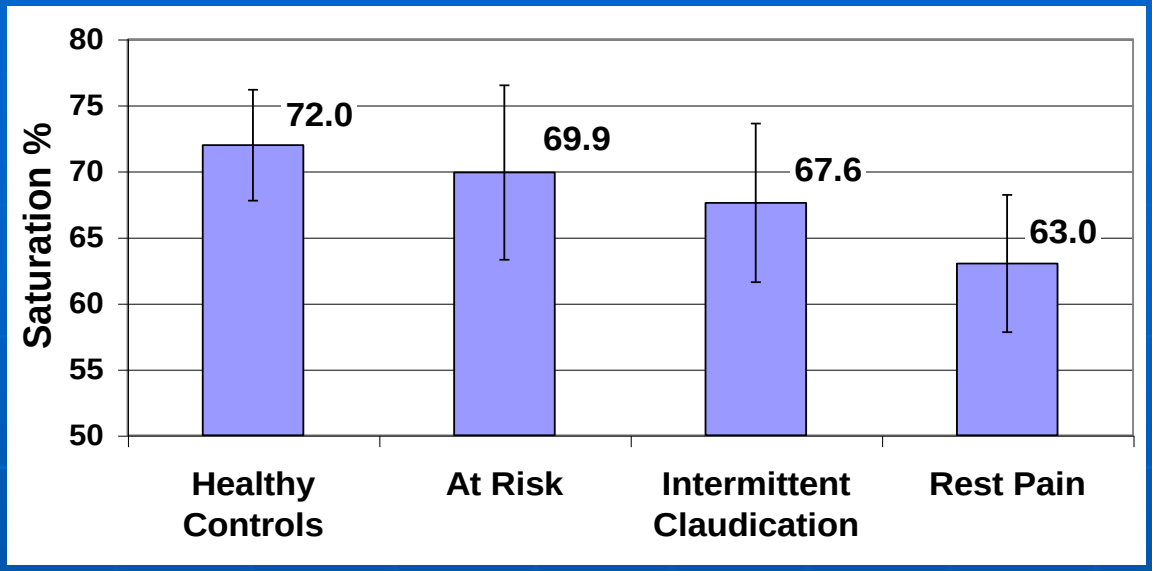
Healthy Controls	17 Subjects
At Risk-	29 Subjects
Intermittent Claudication	27 Subjects
Rest Pain	7 Subjects
Dialysis	15 Subjects

Protocol

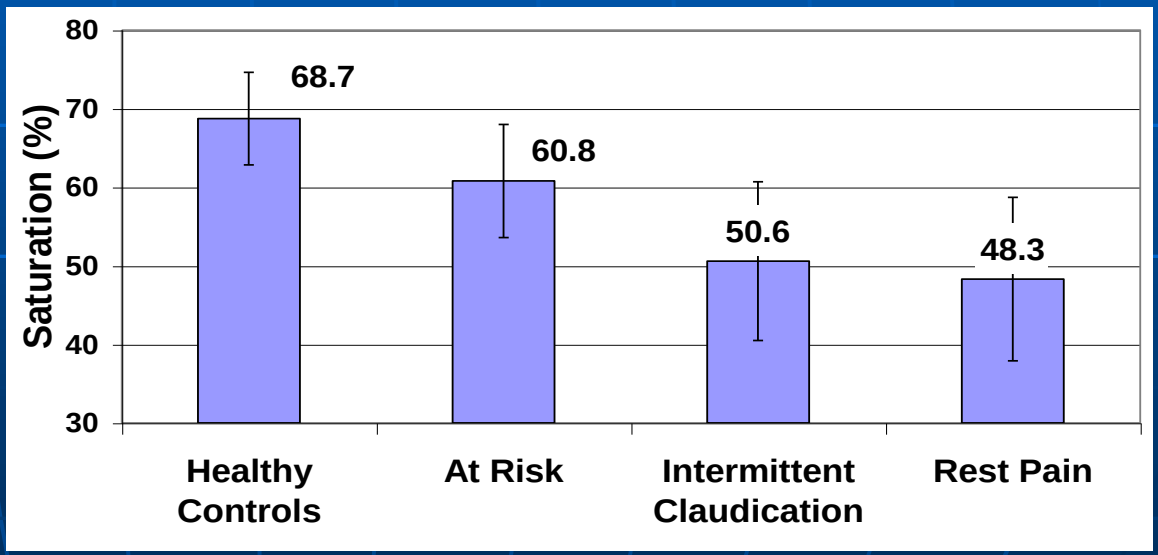
- Oximeter Monitoring Of Both Calves Simultaneously
- Stand
- Walk On Treadmill, 2 MPH at 3% Incline
- Stand

Pre And Post Exercise ABI (Ankle Brachial Index) Also Measured

Tissue Oxygenation at Rest
(Average and Standard Deviation)

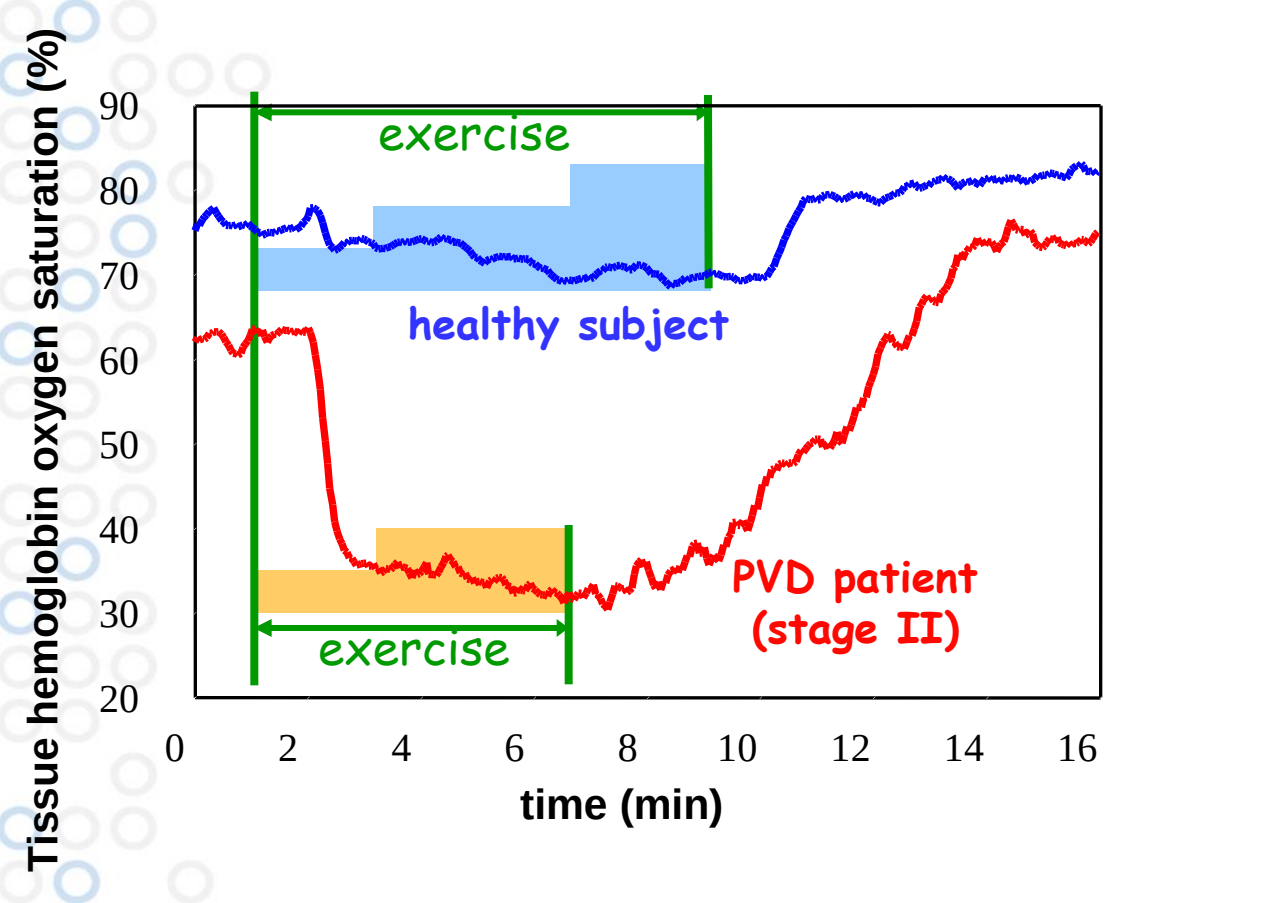


Tissue Oxygenation during Exercise
(Average and Standard Deviation)



Conclusion: There is a correlation between saturation attained during exercise and clinical condition.

Typical hemoglobin saturation traces



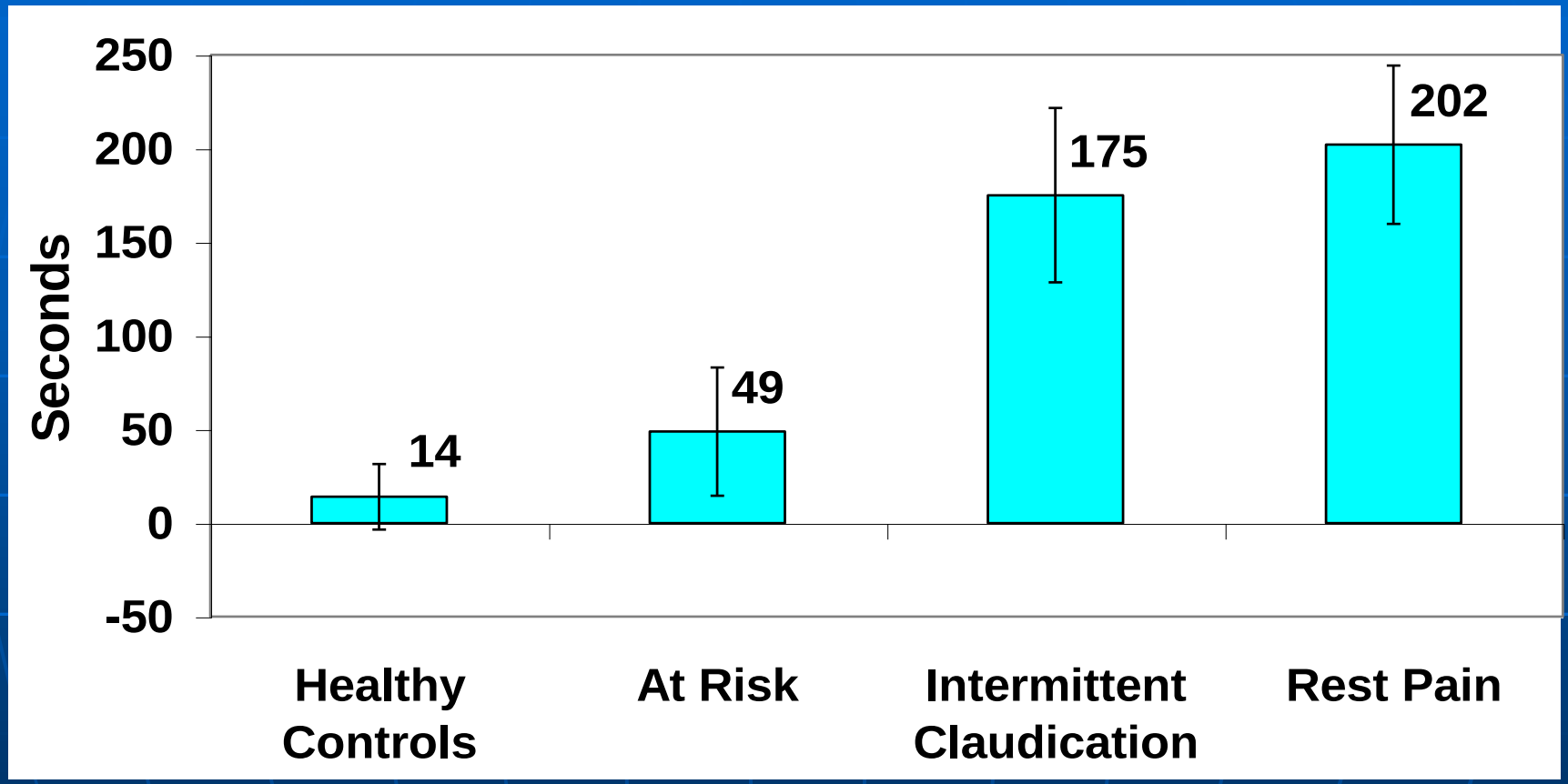
the step function in the shaded areas indicates exercise load (on a stationary bicycle)

patients affected by peripheral vascular disease show:

- ⇨ larger desaturation during exercise
- ⇨ longer recovery time after exercise

Post Exercise Saturation Recovery Time

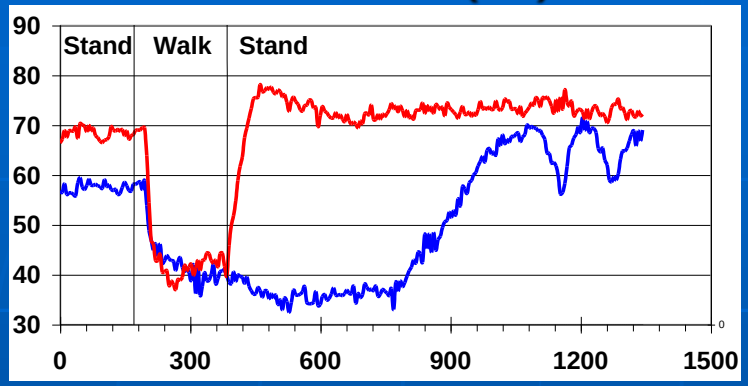
(Average and Standard Deviation)



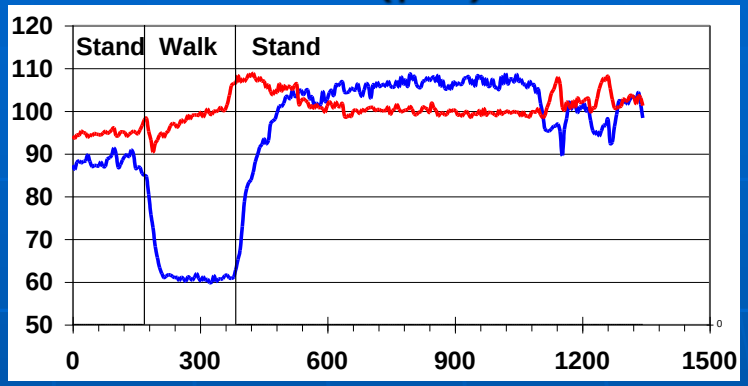
Conclusion: There is a strong correlation between saturation recovery time after exercise and clinical condition

Hemodynamic Analysis Case Study

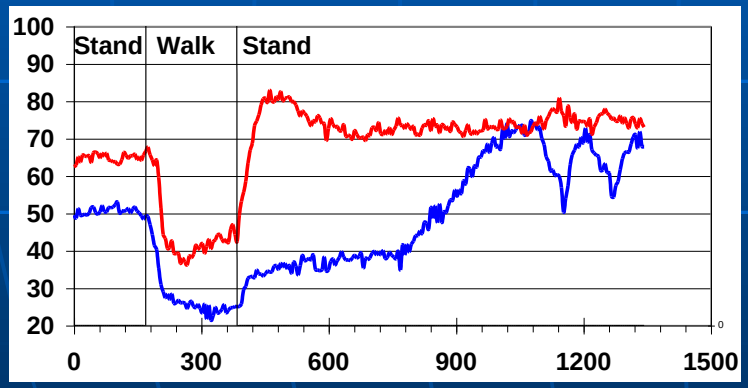
Saturation (%)



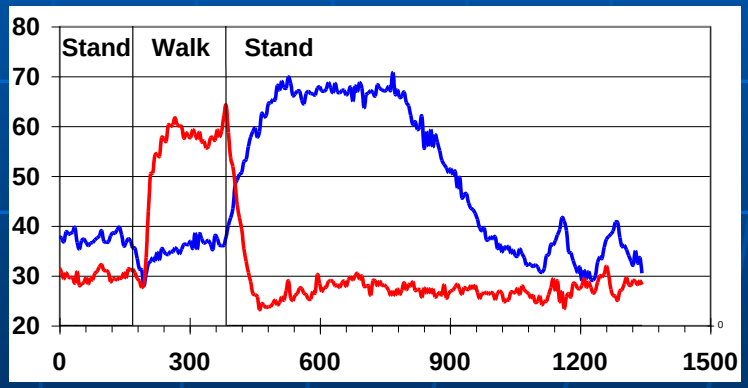
THC (μM)



[Oxy-Hb] (μM)



[Deoxy-Hb] (μM)



Right Calf

Previous Right Side Femoral Artery Bypass

Left Calf

Scheduled For Left Side Femoral Artery Bypass

Angiogram Verified Left Femoral Occlusion

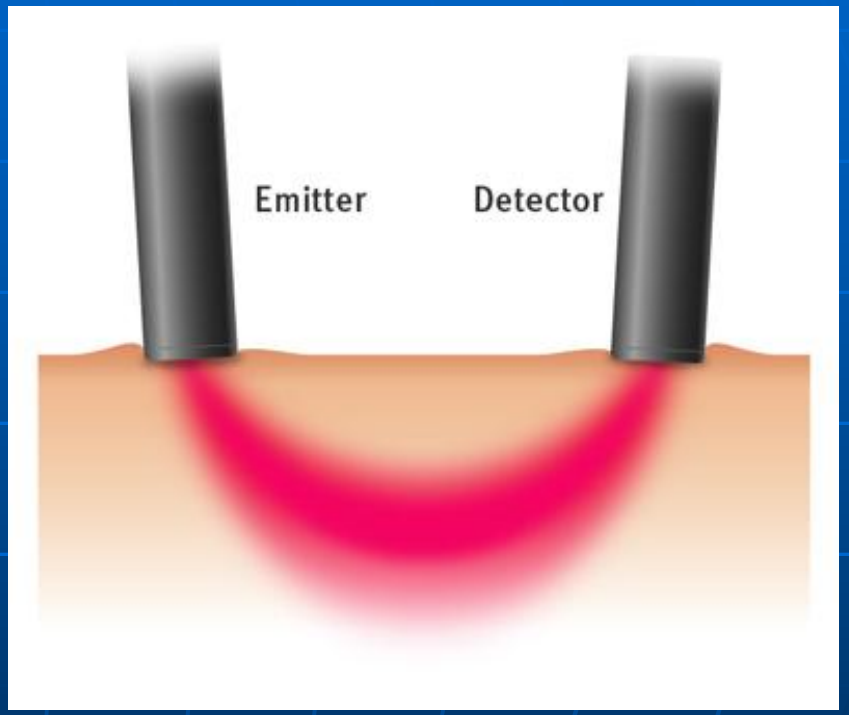
Summary and Conclusions

Baseline Saturation, Exercise Induced De-Saturation, and Post Exercise Saturation Recovery Time all Correlate with Clinical Condition

Exercise Induced Saturation measurements may be effective for PVD assessment

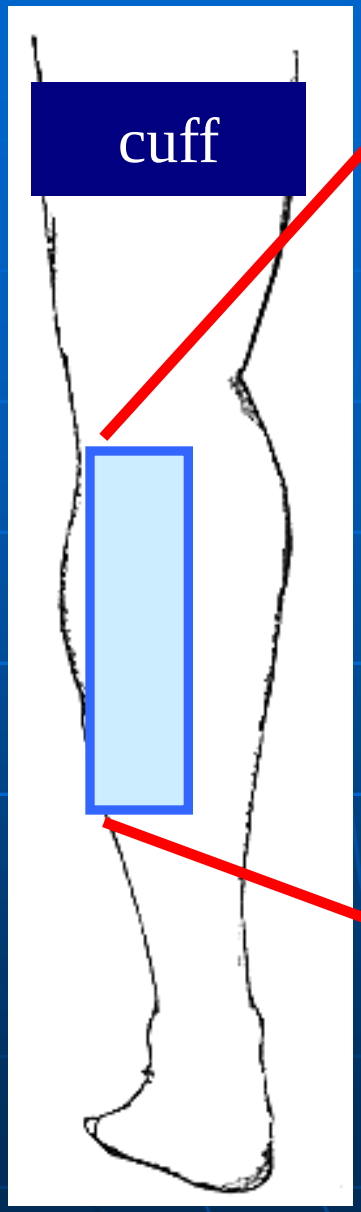
Hemodynamic Analysis of Oximetry Data may provide Diagnostic Information in addition to PVD Assessment

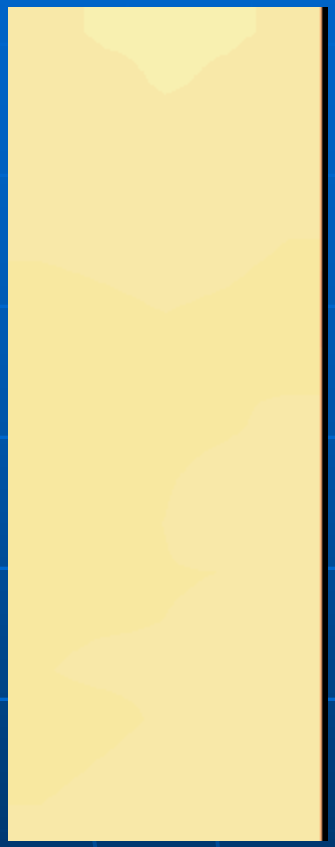
ISS Imagent™

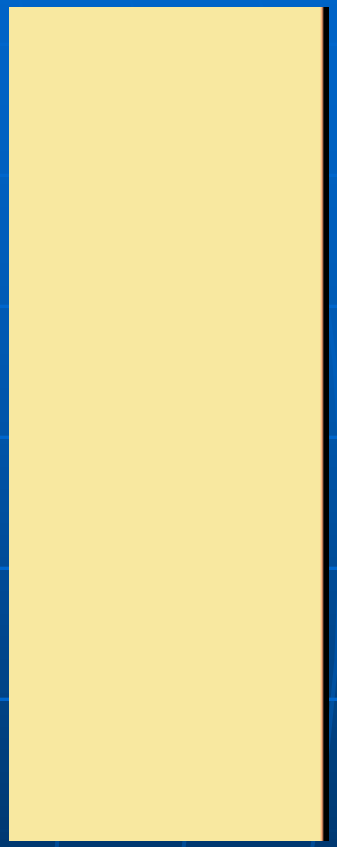


We are able to create functional maps of the tissue

Maps of O_2Hb during a venous occlusion of 3 minutes duration







video runs 3 times faster than real time:

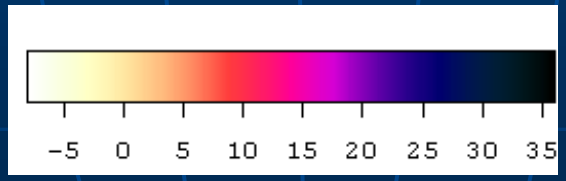
10s start of occlusion

70s end of occlusion

subject with PVD, left leg

subject with mild PVD, right leg

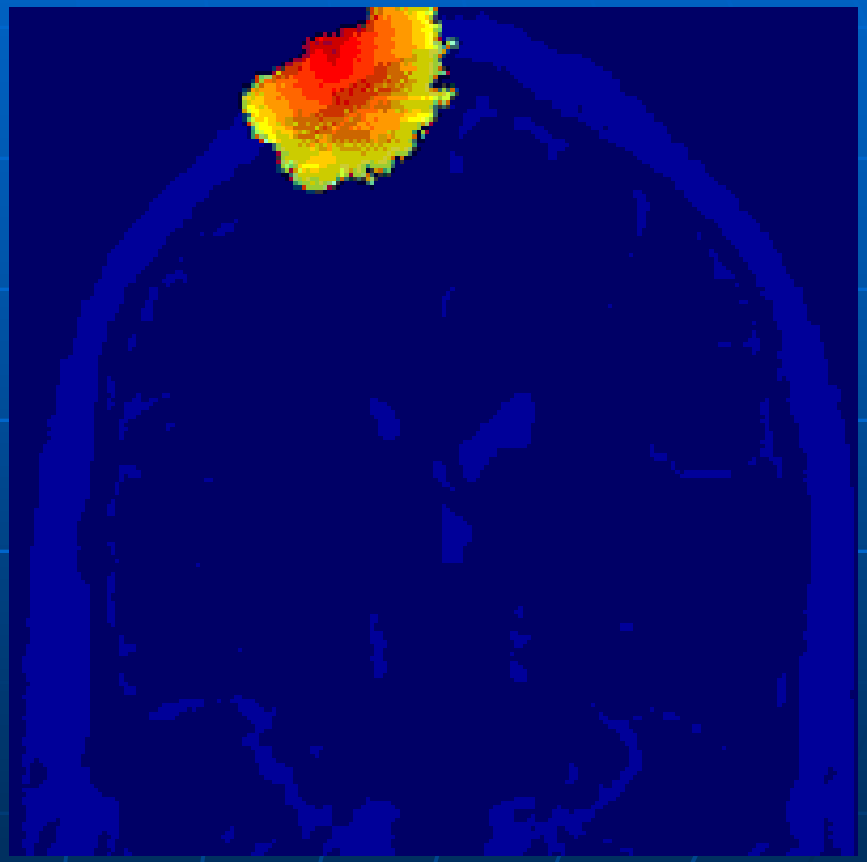
normal subject, right leg



color scale in µM

Why Near-Infrared Spectroscopy and Imaging of Tissues?

- Non-invasive
- Portable
- Cost effective
- Fast
- Reliable



- Real-time monitoring of tissue oxygenation and hemodynamics

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  - Department of Neurosurgery
  - Center for Sleep and Ventilatory Disorders
- **University of California, Irvine**
  - Department Pediatrics
  - Developmental and Cell Biology
  - Beckman Laser Institute
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  - Department of Pediatrics
- **University of Kentucky**
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